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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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June 12, 2014
8:00 a.m.

Holiday Inn Express
20260 Goldenrod Lane
Germantown, Maryland

PANEL MEMBERS:

RICHARD L. PAGE, M.D.	Temporary Panel Chair
RICHARD A. LANGE, M.D., M.B.A.	Voting Member
DAVID C. NAFTEL, Ph.D.	Voting Member
E. MAGNUS OHMAN, M.B., FRCPI, FACC	Voting Member
JOHN C. SOMBERG, M.D.	Voting Member
JOAQUIN CIGARROA, M.D.	Temporary Voting Member
EDWIN C. GRAVEREAUX, M.D.	Temporary Voting Member
JOHN W. HIRSHFELD, JR., M.D.	Temporary Voting Member
DANIEL W. SIMON, M.D.	Temporary Voting Member
DAVID J. SLOTWINER, M.D.	Temporary Voting Member
NAVEEN THURAMALLA, M.S., CCRP	Industry Representative
PHIL POSNER, Ph.D.	Patient Representative
CYNTHIA L. CHAUHAN, M.S.W.	Consumer Representative
JAMIE MAE WATERHOUSE, M.B.A.	Designated Federal Officer

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Patient

TERRENCE HOOVER, D.D.S.
Patient

MICHAEL PERL, D.D.S., MSCD
Patient
(Testimony read by Terrence Hoover, D.D.S.)

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M E E T I N G

(8:00 a.m.)

DR. PAGE: I'd like to call this meeting of the Circulatory System Devices Panel to order. It's now 8:00 a.m.

My name is Richard Page. I will be chairing this Panel. I am a cardiac electrophysiologist, and I am chair of the Department of Medicine at the University of Wisconsin in Madison.

I'd like to start off by having the Panelists introduce themselves. I'll start with Dr. Zuckerman.

DR. ZUCKERMAN: Good morning. My name is Bram Zuckerman. I'm Director, FDA Division of Cardiovascular Devices.

Thank you.

DR. SIMON: Good morning. I'm Dr. Dan Simon, and I'm from New Jersey. I am the Medical Director of the Vascular Access Center of West Orange, New Jersey.

DR. SLOTWINER: Good morning. I'm David Slotwiner. I am a cardiac electrophysiologist, and I practice at North Shore-Long Island Jewish Medical Center and Hofstra School of Medicine.

DR. GRAVEREAUX: Ed Gravereaux, a vascular surgeon at Brigham Women's Hospital in Boston.

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa. I'm an interventional cardiologist and the Clinical Chief of the Knight Cardiovascular

Institute at Oregon Health & Science University.

DR. LANGE: I'm Rick Lange. My background is in interventional cardiology, and I am the vice chairman of medicine at the University of Texas in San Antonio.

MS. WATERHOUSE: Good morning. I'm Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. NAFTEL: My name is David Naftel. I am a Professor of Surgery and Biostatistics at the University of Alabama at Birmingham.

DR. HIRSHFELD: I'm John Hirshfeld. I am an interventional cardiologist at the University of Pennsylvania.

DR. SOMBERG: My name is John Somberg. I am a Professor of Medicine and Pharmacology at Rush University and practice cardiology.

DR. POSNER: I'm Phil Posner. I'm a patient rep and retired cardiac electrophysiologist in physiology and pharmacology.

MS. CHAUHAN: Cynthia Chauhan, Consumer Rep.

MR. THURAMALLA: I'm Naveen Thuramalla. I am the Vice President of Engineering and Clinical Studies at Transonic. I'll be serving as the Industry Representative.

Thank you.

DR. PAGE: Thank you.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add

that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application of the Lutonix 035 Drug-Coated Balloon PTA Catheter.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Jamie Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application for the Lutonix 035 Drug-Coated Balloon PTA Catheter sponsored by Lutonix. The Lutonix 035 Drug-Coated Balloon PTA Catheter, or the Lutonix DCB, is an over-the-wire percutaneous transluminal angioplasty catheter with a paclitaxel-based drug coating on the surface of the balloon. The proposed indications for use are for improving luminal diameter for the

treatment of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S. Code Section 208.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Transonic Systems.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I

appoint the following individuals as voting members of the Circulatory System Devices Panel for the duration of this meeting on June 12th, 2014:

Dr. Hirshfeld, Dr. Cigarroa, Dr. Gravereaux, Dr. Slotwiner, Dr. Simon.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Dr. Richard Page to act as temporary chairperson for the duration of this meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on May 29th, 2014.

For the duration of the Circulatory System Devices Panel meeting on June 12th, 2014, Dr. Philip Posner has been appointed as a Temporary Non-Voting Member. For the record, Dr. Posner serves as a patient representative to the Peripheral and Central Nervous System Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Associate Commissioner for Special Medical Programs, on May 30th, 2014.

Before I turn the meeting back over to Dr. Page, I would like to

make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Susan Laine.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you.

DR. PAGE: Thank you very much.

Before we get started, I'd like to just remind the Panel of a couple things. One is that if you are speaking, please press your microphone

before you start speaking. Please wait to be called on, and don't press it until you've been called on, because the more microphones lit up, the harder the acoustics are.

The other thing to just remind the Panel of is that everything is in the minutes. I ask for no side conversations. Everything you say is really important to us, and we want you to be able to say it on the record, as part of the Panel. So, again, I ask for you to abide by that rule.

And, finally, in terms of time, I'll just remind the Sponsor and the FDA that we are setting a timer, and we ask everyone to stay within their allotted time period.

So with that, it's my pleasure to request for the Sponsor to prepare and present their presentation to us. And as mentioned, you have 90 minutes.

Thank you.

DR. DeFORD: Thank you and good morning, Mr. Chairman, members of the Committee, and members of the Food and Drug Administration. My name is John De Ford. I'm the Senior Vice President for Science, Technology and Clinical Affairs for C.R. Bard. Lutonix is a wholly owned subsidiary of C.R. Bard.

I'd like to thank the FDA and the Committee for the opportunity to present data on the Lutonix drug-coated balloon, also known as DCB, a technology for the treatment of peripheral artery disease, or PAD, specifically

in the femoropopliteal artery.

The Lutonix DCB combines a proven percutaneous transluminal angioplasty device, or PTA, with a proven anti-restenotic agent, paclitaxel. Paclitaxel has been approved in the U.S. since 2004, in coronary and peripheral drug-coated stents such as Taxus and Zilver PTX. It has also been an approved chemotherapy agent since 1992.

The safety profile and mechanism of action for paclitaxel is well characterized. Paclitaxel stabilizes cellular microtubules and inhibits cell division, migration, and secretion. Studies have shown that when applied directly to the artery, paclitaxel inhibits smooth muscle cell proliferation and neointimal hyperplasia.

Let me walk you through the DCB design requirements.

When developing a new technology like a drug-coated balloon, it's critical to lay out the key design requirements of the product prior to starting the program. We identified four key requirements necessary for a drug-coated balloon to be successful.

First, you need a proven balloon platform. Then the coating needs to be applied to the balloon so that it is uniform across the entire working surface of the balloon. Third, the coating must be durable and robust, such that it would adhere to the surface of the balloon during routine handling by the physician during the procedure. And, finally, the coating will need to release from the balloon surface at time of inflation at the lesion and

transfer the drug to the vessel wall.

The Lutonix DCB was the product of the design elements I just mentioned. Extensive preclinical research was performed to optimize the formulation. In fact, over 250 formulations of drug and carrier combinations were studied to find a formulation that allows the drug to adhere to the balloon, yet also allows the drug to transfer to the lesion site upon short-term contact during inflation.

Lutonix DCB utilizes a paclitaxel dose of 2 $\mu g/mm^2$. In addition, the coating contains a carrier combining polysorbate and sorbitol. Polysorbate and sorbitol are known excipients in products currently approved for intravenous use in the U.S. Combining these excipients with paclitaxel resulted in a stable coating that delivered therapeutic drug levels to target lesions in preclinical models.

Let me show you how the DCB actually works. This video describes the use of the Lutonix drug-coated balloon. After vessel preparation, like any other angioplasty balloon, the procedure begins, if required, with the introduction of a guide wire which is placed across the lesion. The Lutonix drug-coated balloon is advanced and inflated for a minimum of 30 seconds. Upon balloon inflation, paclitaxel transfers to the vessel wall with the aid of the carrier.

Preclinical data demonstrates sustained drug retention in arterial wall tissue at concentrations that inhibit smooth muscle cell

proliferation.

The Lutonix DCB has been in development since 2007. In collaboration with the FDA and clinical thought leaders, the first femoropopliteal human study, LEVANT 1, was initiated in 2009. It was a randomized trial of 101 patients that provided initial data on safety and efficacy. LEVANT 1 showed that the Lutonix DCB arm had significantly less late luminal loss compared to the control at six months. In addition, the Lutonix DCB demonstrated comparable safety to conventional PTA.

CE mark was received in 2010, and in 2011 our pivotal study, LEVANT 2, was initiated. LEVANT 2 is a global, prospective, multicenter, single-blind randomized clinical trial designed to confirm the safety and efficacy of the Lutonix DCB.

In 2012, we initiated the LEVANT 2 safety registry, which is a continuation of the LEVANT 2 DCB arm of the pivotal study. Enrollment for the safety registry was completed in July 2013. There is also an ongoing superficial femoral artery and popliteal global registry which can enroll up 1,000 patients.

Through these studies, Lutonix has amassed data on the drug-coated balloon in over 1,500 patients, with follow-up to be continued to five years.

Drug-coated balloons have been available to patients in Europe for over five years. The Lutonix DCB became available to patients outside the

United States in July 2012, and to date, over 10,000 devices have been used in the SFA and popliteal arteries. Today, there are more than eight different peripheral DCBs approved outside the U.S., with over 80,000 balloons being used in 2013.

Today's presentation will focus on data from our pivotal LEVANT 2 randomized study. To date, LEVANT 2 is the largest randomized study evaluating the use of drug-coated balloons in the peripheral vasculature.

As mentioned earlier, an angioplasty procedure dilates the stenosed segment of the vessel. This study was designed to evaluate the improvement in 12-month primary patency of the treated femoropopliteal artery using a drug-coated balloon when compared to angioplasty alone.

The LEVANT 2 study was also designed to demonstrate non-inferior safety compared to PTA. Both primary endpoints were met, demonstrating superior primary patency and non-inferior safety to standard PTA.

If approved, the Lutonix DCB would be the first technology of its kind in the U.S.

These indications are used to support our proposed indication. A typical indication for a PTA catheter is for improving luminal diameter and is very broad for treating a wide range of vessel types and sizes. The Lutonix DCB is proposed to have the same indication as PTA with specific lesion types,

length, and diameter. Specifically, the Lutonix drug-coated balloon PTA catheter is indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions ≤ 15 cm in length in the native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.

Here is our agenda for today. Dr. Kenneth Rosenfield from Massachusetts General Hospital will discuss the need for the Lutonix DCB, summarize the design of the LEVANT 2 study, and present demographic and procedural results. Dr. Michael Jaff, medical director of the vascular ultrasound core laboratory used in support of this trial, will then present the efficacy results. Dr. Gary Ansel from Riverside Methodist Hospital will then discuss the safety results. Mr. Chris Mullin will present our findings on subgroup interactions. I will return briefly to discuss our post-approval plan. And, finically, Dr. Jihad Mustapha will close with the benefit/risk assessment.

We have additional experts to answer to your questions.

All of our presenters have been compensated for their time and travel for today's meeting, with the exception of Dr. Jaff, who will discuss his disclosures at the beginning of his presentation.

Thank you. And I now invite Dr. Rosenfield to the lectern.

DR. ROSENFIELD: Good morning. My name is Kenneth Rosenfield. I am the section head for vascular medicine and intervention at Massachusetts General Hospital.

Peripheral artery disease is a condition characterized by a buildup of plaque in the non-coronary blood vessels, which results in narrowed arteries and reduction in blood flow. Most commonly, it affects blood flow to the lower extremities. This can result in disabling leg pain when walking, called intermittent claudication, and can even lead to amputation.

PAD is a common disease affecting up to eight million Americans and is more common in patients with diabetes. The prevalence is higher in Americans over the age of 70, affecting nearly 20%. Importantly, PAD is a marker for cardiac disease. In fact, death from cardiovascular disease is sixfold greater in patients with PAD compared to patients without PAD.

The femoropopliteal artery is the most commonly diseased vessel in the peripheral circulation and is the most frequent site of lower limb intervention.

Symptomatic PAD doesn't just result in minor discomfort or inconvenience. In fact, the impact on patients' quality of life is substantial. Symptoms can advance to the point where the patient cannot even perform their routine daily activities such as going to the mailbox, shopping, or even walking around their homes. In some instances, the narrowing may progress enough to cause critical limb ischemia, characterized by either pain at rest, ulcers on the feet or toes, or gangrene.

Patients with diabetes are especially at risk for critical limb

ischemia. It occurs in approximately 15% of patients with diabetes, further elevating their risk of amputation.

So what does this patient population with PAD look like with respect to cardiovascular outcomes?

The REACH study was a prospective cohort of over 68,000 patients, enrolled across 44 countries, with either established atherosclerotic arterial disease or at least three risk factors for atherothrombosis. The peripheral artery disease cohort is comprised of over 8,500 patients with symptomatic PAD. It was this patient population that was studied in the LEVANT 2 trial.

Most of the people who suffer from PAD have other challenging comorbid conditions such as obesity, hypertension, and diabetes. They comprise a vulnerable patient population that is already dealing with complex treatment regimens and frequent visits to the hospital or clinician. At one year, mortality is nearly 4%, MACE is over 5%, and cardiovascular hospitalization is over 21%.

The femoropopliteal artery is the most commonly diseased vessel in the peripheral circulation. This artery starts at the hip and extends to below the knee joint. There are unique and complex characteristics of this artery. The femoropopliteal segment is exposed to many rigorous forces, which includes shortening, elongation, torsion, flexion, and bending at the knee joint. It is also vulnerable to external compression. These forces add to

the challenges of treating this vessel initially and to obtaining a durable long-term result.

So let's look closer at this artery. The image on the left demonstrates a patent femoropopliteal artery as seen on an angiographic image. Note that the vessel is widely patent; no narrowings are seen.

The image on the right is from a 64-year-old male smoker who has pain in his calf after walking a short distance. You can see that the artery has multiple high-grade stenoses that are compromising flow to the lower extremity. This is what we often see in patients with SFA disease who have severe or disabling symptoms of claudication.

There are noninvasive and invasive femoropopliteal treatment options available. Each has associated limitations. The most conservative approach to treatment is to employ risk factor modification such as smoking cessation and dietary measures in conjunction with regular exercise. Pharmacotherapy can be useful in some patients, but there is only a single medication, called cilostazol, that is effective.

Unfortunately, these treatment options are limited. While smoking cessation, dietary modification, and exercise are cornerstones of therapy for all patients with PAD, maintaining patient compliance has been challenging. Additionally, up to 30% of patients are intolerant of medication, and it is ineffective in up to half of patients.

At the other end of the treatment spectrum, surgical bypass

can be used for patients that fail conservative therapy, but it is an option that is associated with significant risk, morbidity, and even mortality. Accordingly, surgery is generally reserved for patients with severe symptoms or those at risk for amputation who have limited or no percutaneous options.

For most patients who fail conservative therapy alone, interventionalists and surgeons will typically offer a lower-risk percutaneous endovascular procedure as the initial treatment option. The ability to restore blood flow with a less invasive percutaneous procedure allows for treatment of patients with less severe but still lifestyle-limiting symptoms.

As we talk about endovascular treatments, we use the term "patency" to describe how open or unobstructed an artery is. When we relieve the obstruction with a procedure, we aim to restore patency. Thus, patency is the primary goal of any endovascular treatment for femoropopliteal disease and is typically used as the endpoint in device trials.

Patency is a clinically relevant and appropriate assessment of procedural outcome. It is a concrete and quantifiable measure of the continued relief of arterial obstruction at the treatment site. Patency ends when significant obstruction redevelops. Typically, this is associated with the recurrence of patient symptoms.

For these reasons, modern clinical trials of endovascular devices used to treat the femoropopliteal artery and recent FDA IDE studies, shown here, all used primary patency as the primary efficacy endpoint. As I

will discuss, in collaboration with the FDA, Lutonix also selected primary patency as the measure of efficacy.

The endovascular approach is typically the first and preferred method to treat patients with symptomatic PAD. PTA has been the cornerstone of endovascular therapy for at least the last half century. PTA is, by consensus, the first-line therapy and standard of care for PAD, as delineated in the American College of Cardiology and American Heart Association 2011 PAD guideline statement. However, PTA is challenged by its relative lack of durable patency.

In a recent meta-analysis, the one-year patency of PTA without repeat intervention is estimated to be as low as 33%. The use of stents has been added to PTA in an effort to improve patency and reduce the need for repeat procedures. One-year patency rates for bare-metal or drug-eluting stents after PTA range from 63% to 81%. Stenting is thus recommended when there is significant residual stenosis after PTA.

With a favorable patency of stents compared to standard PTA, why seek an additional option? Well, as I noted earlier, the femoropopliteal segment is subject to unique forces. As a result, stents may fracture and lead to vessel injury. In addition, the presence of a foreign body can be an ongoing stimulus for restenosis. Stents may also jail collaterals, which can compromise distal blood flow should they become occluded. Future surgical options may also be limited as well, because it can be challenging to operate

on a stented vessel.

Furthermore, in-stent restenosis, when it occurs, is extremely challenging to treat. The only currently approved treatment is balloon dilatation alone, which is not particularly effective. The popliteal artery, which is located behind the knee, is subject to more flexion and is considered to be a "no stent zone." As you can see, there are many reasons to avoid the use of a stent during revascularization.

To summarize, there remains a significant clinical need for a device that is able to achieve more durable patency than standard PTA, without leaving behind a permanent implant. Non-implant based endovascular therapies provide clinicians with a first-line treatment in the difficult anatomy of the femoropopliteal artery, while leaving future treatment options open. These therapies also open the door for treatment of a broader patient population, including those with lesions in the so-called "no stent zones."

With that background and on behalf of the LEVANT 2 investigators, I'm pleased to present to you the study design and baseline patient characteristics.

LEVANT 2 is a prospective, single-blind study with patients randomized 2:1 to treatment with the Lutonix DCB or standard PTA for lesions in the femoropopliteal artery. There are 54 sites, 42 in the U.S. and 12 in Europe. Patients were consented for clinical visits at 6, 12, and 24

months and telephone follow-up out to five years, which is currently ongoing. LEVANT 2 was carefully designed to avoid potential confounders typically seen in femoropopliteal clinical trials.

I'd like to highlight three important design objectives we combined in the LEVANT 2 study. These were, first, to study the additional effect of drug in angioplasty; second, to minimize potential bias in the clinical evaluation that leads to re-intervention; and, third, to assess the durability of treatment.

First, we wanted to specifically evaluate the enhancement of standard angioplasty by adding a drug with anti-restenotic properties. Stenting would have confounded our ability to isolate that effect; therefore, we sought to minimize stenting. Our strategy to minimize stenting was incorporated in the study design.

Here is the LEVANT 2 study flow. Prior to any randomization, patients were required to have a successful pre-dilatation of the target lesion using a standard balloon sized approximately 1 mm less than the reference vessel. If patients had either a major flow-limiting dissection or a residual stenosis > 70% after the pre-dilatation, then they were not randomized and instead they were treated per standard practice. These patients were then followed for 30 days for safety events.

If there was residual stenosis < 70% and there was absence of a flow-limiting dissection, or if the lesion was not appropriate for stenting due

to proximity to the knee joint, patients were then randomized to either Lutonix DCB or standard PTA.

Criteria for bailout stenting were well defined and rigorous. Bailout stenting was allowed for either arm only if the following were present: greater than 50% residual diameter stenosis or flow-limiting dissection, and greater than 10 mm/Hg pressure gradient refractory to prolonged dilatation.

Second, as mentioned, we tried to remove potential bias during follow-up. The decision whether or not to perform a target lesion revascularization in a given patient is a subjective one. We know, during follow-up, awareness of the patient's randomization assignment and results of the diagnostic testing can influence the decision to re-intervene. Our goal was to have decisions regarding repeat revascularization based purely on clinical grounds. Therefore, we established a unique blinding strategy previously not incorporated in femoropopliteal studies. This was accomplished through a careful blinding strategy, as shown here.

The physician conducting the follow-up visit was blinded to the treatment assignment and was a different individual than the physician who performed the index procedure. Unfortunately, the physician performing the procedure could not be blinded because the drug-coated balloon looks different than an uncoated balloon, and though attempts were made to create visually identical balloons, it was not possible due to the appearance

of the coating.

In addition, the patients, the core labs, and duplex ultrasound technicians were blinded at all time points. The follow-up physician was blinded to both the treatment arm and the duplex ultrasound results. This was to ensure the evaluation of the clinical symptoms was unbiased.

In fact, as we'll discuss in more detail later, among patients with binary restenosis or those with worsening Rutherford class, both Lutonix DCB and standard PTA groups had the same rate of re-intervention. This has not been seen in any other peripheral randomized trial to date, and these observations confirm that our study design did indeed minimize bias in the clinical decision to re-intervene.

As for this last objective, LEVANT 2 did not count bailout stenting as a failure, unlike recent randomized femoropopliteal stent studies. For example, in RESILIENT and Zilver PTX, the stent group had a 40% to 50% primary efficacy endpoint advantage immediately after the index procedure due to this classification of bailout stenting in the control PTA arm.

I would like to now review the study inclusion and exclusion criteria.

The following were the key clinical and angiographic inclusion criteria. Patients had to be male or non-pregnant females 18 years of age or older and symptomatic with Rutherford Category 2 to 4. Rutherford categorization is a commonly used measurement that defines peripheral

vascular disease severity on a scale of 0 to 6, where 0 indicates a patient with no symptoms and 6 indicates a patient with major tissue loss and gangrene. Patients had to have an angiographically significant lesion, defined as diameter stenosis ≥ 70%, a target lesion length ≤ 15 cm, and reference vessel diameter of 4 mm to 6 mm.

Patients were excluded if they had a hemorrhagic stroke three months prior to the procedure, or if they had chronic kidney disease with a GFR < 30 mL/dL. Patients were also excluded if they had a life expectancy < 5 years, were unable to take the study medications, or had prior vascular surgery involving the index limb.

The study had a clinical events committee, or CEC, and a data monitoring committee, or DMC. Both committees were comprised of independent physicians with expertise in peripheral vascular disease and cardiovascular medicine. The CEC, which was blinded to the patients' randomization assignment, reviewed and adjudicated all clinical events that occurred during the trial. They also determined seriousness and if the event was procedure or device related. The DMC was responsible for oversight and safety monitoring.

Both core labs were blinded to the randomization assignment of the patient. The core lab for duplex ultrasound was VasCore, run by Dr. Michael Jaff, who will present the efficacy results later in this presentation. The angiography core lab was SynvaCor.

With these design elements in mind, let's discuss the endpoints.

The efficacy endpoint was primary patency of the target lesion at 12 months. Patency was defined by two parameters, both of which must have been satisfied: first, the absence of target lesion binary restenosis by duplex ultrasound, as adjudicated by the core lab; second, freedom from TLR, as adjudicated by the CEC.

The safety endpoint was a composite of freedom from all-cause perioperative death and freedom at 12 months from index limb amputation, index limb re-intervention, or index limb-related death.

The study also had several secondary efficacy and safety endpoints. These endpoints were not considered in the determination of sample size, so power is limited. A subset of secondary endpoints was prespecified for hierarchical testing, including target lesion revascularization and target vessel revascularization.

Other secondary endpoints were examined to provide additional clinical information, including patient-reported outcomes and physical function at baseline, 6, and 12 months. These included Rutherford classification and response to the Walking Impairment Questionnaire, which measured the patient's own assessment of their walking performance. Two quality of life surveys, the SF-36 and the EQ-5D, were also completed. Other endpoints included death, amputation, and limb re-intervention.

The study was powered for both the primary efficacy and primary safety endpoint. For the study to achieve 90% power, 476 patients were required. The sample size accounted for an expected 15% loss of patients from the primary analysis due to either study exits or missing imaging data.

A common protocol with identical inclusion and exclusion criteria was employed at all clinical sites. Patients were block randomized within study sites, and the procedures and instruments used for evaluation were identical in the U.S. and Europe. All endpoints were adjudicated by the same core lab and the same CEC. We incorporated these design elements to ensure poolability.

With that background on design and study conduct, I will now present the baseline patient characteristics and procedural data for LEVANT 2.

Here again you see the flow diagram for patients entered into the study. Five hundred and forty-three patients were enrolled. Each site was to perform a proctored Lutonix DCB procedure prior to enrolling a randomized patient. These roll-in patients were intended to familiarize site personnel with the clinical trial data, collection process, and the usage of DCB. There were 53 roll-in patients plus three live demonstration cases performed during conferences in Europe that were also categorized as roll-ins.

Consented patients underwent the pre-dilatation previously described. After pre-dilatation, only 11 patients were identified with suboptimal PTA who were deemed unlikely to achieve a successful result with balloon angioplasty alone. These patients were not randomized. Four hundred and seventy-six patients were randomized, 316 to the Lutonix DCB and 160 to standard PTA.

The primary analysis dataset was prespecified. It was comprised of all patients, as randomized, that were evaluable at 12 months. This is the intention-to-treat group, or ITT. And the impact of missing data was assessed by tipping point, worst-case, and time-to-event analyses. Remarkably, in this study, all subjects received their assigned treatment. So the as-treated group (AT) is identical to the intention-to-treat group. The primary and secondary analyses are performed on this ITT population.

This table shows selected patient baseline demographic data and medical history. The randomized groups were well matched. The mean age was 68 years, the majority of patients were male, and approximately one-third were current smokers. Approximately 43% had diabetes, and the majority had dyslipidemia and hypertension. Nearly half had a history of coronary artery disease.

This table shows two common measures of peripheral vascular disease severity: Rutherford classification and ankle-brachial index, or ABI. Ankle-brachial index is a noninvasive hemodynamic measurement used as an

indicator of severity of PAD. The baseline distribution of Rutherford classification was similar in both arms. The majority of patients had moderate or severe claudication. Eight percent of patients in each group had ischemic rest pain or Rutherford Category 4. There were no differences in ABI between the groups.

Here we see important lesion characteristics as adjudicated by the angiographic core lab. The average lesion length was greater than 62 mm and the average treated length was 108 mm. Nearly two-thirds of the patients had calcification, and it was severe in about 10%. In addition, 21% of lesions were total occlusions.

In the next slide, I will show you procedural details.

There was a significantly higher rate of grade C dissection after treatment with standard PTA than Lutonix DCB. This resulted in a higher bailout stent rate of 6.9% in the standard PTA arm compared to 2.5% in the Lutonix DCB arm. Consistent with the intent of the study design, although the rates were different, the overall rate of bailout stenting was quite low.

In addition, a greater number of balloons were used in the DCB arm. This is due to two reasons: first, a limited number of DCB lengths were available for the trial; and, second, unlike a PTA balloon, a DCB could only be inflated once. As you can see, the inflation time was greater for the PTA arm on a per-balloon basis. However, total inflation time per patient was not statistically different.

Also, the average pressure used in the PTA arm was statistically greater. However, in this arm of the study, the clinician was allowed to use any commercially available PTA catheter. This difference in inflation pressure is largely explained by the variability of nominal inflation pressure required to achieve the desired diameter in these balloons, while the treatment arm had specific sizes of the Lutonix DCB available.

The duration of the procedure and the device success rates were comparable between the two arms, and the final procedure results were similar. Final percent diameter stenosis was 21% for both arms, and procedural success, defined as 30% or less residual stenosis without a serious adverse event, was comparable. In addition, there was a significant difference in geographic miss, with a larger number of occurrences observed in the PTA arm.

Let me introduce you to this concept. It is important to understand the definition of geographic miss used in LEVANT 2. Geographic miss refers to any area of the vessel that was treated with inflation pre- or post-dilatation but was not covered by the DCB or standard balloon. In the DCB arm, this makes perfect sense, as the intent was to deliver drug to the entire dilated segment and not doing so would constitute a geographic miss.

However, the importance of covering the entire dilated segment is not relevant in a standard PTA arm as long as the lesion is well treated. In fact, in best clinical practice, clinicians would specifically not

reinflate a balloon in a well-treated segment. Therefore, even though we analyze geographic miss using the same definition for both groups, it is not clinically meaningful in the standard PTA patients. Irrespective of geographic miss, best clinical practice was applied in both arms of this trial.

Here are a series of angiograms explaining this concept. On the left you see the stenotic lesion at the beginning of the procedure. The lesion is pre-dilated per the protocol, and the green lines indicate the margins of the treated segment. The result shows the lesion now meets eligibility criteria, and the patient is randomized.

The lesion is then treated with a study device -- in this case, a standard PTA balloon -- with margins indicated by the blue lines. The final result is acceptable, and the patient is followed throughout the study. As you can see, there was an area, defined by the bracket, that was treated with a pre-dilatation balloon but not covered by the study device, and this was identified by the core lab as a 5 mm segment of geographic miss. If the study device had been a DCB, this area would not have received a drug.

From my perspective, the area of the pre-dilated segment clearly did not require additional dilatation to achieve a good result, and I understand why the treating clinician would not have gone back in and treated that very small area a second time, knowing the treatment balloon was standard PTA.

Since the core lab was blinded, geographic miss assessments

were obtained for all patients. The treating clinicians, who were unblinded to the treatment, did not always take additional steps to cover the entire pre-dilatation segment for standard PTA patients if there was no residual stenosis. The interventionalists would not be concerned about delivering drug, and there would be no reason otherwise to re-dilate an already open vessel.

Please note that the procedural outcome was the same for DCB and PTA. The final percent diameter stenosis post-treatment and the procedural success were not statistically different. More importantly, the same was true for the impact of geographic miss. The final percent diameter stenosis for patients with and without geographic miss were not statistically different.

Thank you. Dr. Jaff will now present the efficacy results.

DR. JAFF: Thanks, Dr. Rosenfield.

Good morning, ladies and gentlemen. My name is Michael Jaff. Before I present the efficacy results, I would like the Committee to note that although I am the medical director of VasCore, the vascular ultrasound core laboratory used in this trial, all contractual funds paid directly from Lutonix to Mass General Physicians Organization were done for VasCore services. My compensation from Mass General Hospital is not determined by the volume of trials in which VasCore participates. I have not received any personal compensation from Lutonix for my participation in this clinical trial. I also

have not been compensated by Lutonix for my time, travel, or expenses to be present here today.

Having completed my disclosure, I'm pleased to present to you the efficacy results of this study. I'll first review how we use duplex ultrasound to measure patency and the rationale for using primary patency as the endpoint. Then I will discuss the primary efficacy per-protocol and subgroup results. Finally, I will review the secondary efficacy endpoints.

Let me show you why we use primary patency as the endpoint and how we use duplex ultrasonography to measure patency.

As a reminder, this study was designed to evaluate patency of the artery after angioplasty with and without a drug coating.

Primary patency is defined as the absence of binary restenosis based on duplex ultrasound, as adjudicated by the core lab, and freedom from TLR, as adjudicated by the CEC, through the 12-month follow-up window. It was a superiority test on the prespecified analysis group, or ITT, with a two-sided alpha of 0.05.

We use duplex ultrasound to measure vessel patency, as is routinely used in clinical practice to follow patients after an endovascular intervention. I would like to show you an example of how arterial duplex ultrasound is used to image arteries noninvasively before and after treatment.

This is a gray scale image of a superficial femoral artery. In this

image, as with the others I will show you, blood is flowing from left to right.

This is a color arterial duplex ultrasound image demonstrating spectral waveforms and velocities within a normal arterial segment. For those of you who don't regularly view these images, let me orient you.

The vertical line emanating from the top and coursing down depicts the path of the ultrasound beam. The two parallel horizontal lines within the red arterial image shows where the ultrasound beam is being concentrated. The parallel line bisects those two lines, determining the Doppler angle. This is a critical component of Doppler ultrasound physics to provide an accurate determination of peak systolic velocity.

As a reminder, the duplex ultrasound is performed during follow-up visits, so the balloon is not present in the artery during the ultrasound.

This is a healthy vessel, as you can see from the duplex spectral waveform on the bottom of this slide, which shows a normal peak systolic velocity of 78.6 cm/s.

This image demonstrates sampling within the area of stenosis. In contrast to the previous image, there are multiple different colors within the artery, suggesting turbulence and increased peak systolic velocities. Here, the duplex velocity is 333 cm/s.

This image is distal to the image where the stenosis was identified. You'll notice a markedly abnormal Doppler waveform with a

chaotic post-stenotic turbulent appearance. We calculated the peak systolic velocity ratio by dividing 333 cm/s by 78.6 cm/s to result in a systolic velocity ratio of 4.3, which indicates significant stenosis.

As I just described, duplex ultrasonography provides a quantitative measure of flow velocities within a stenosis as compared to a normal segment of artery proximal to the stenosis. We chose a binary endpoint of patency because of the high correlation of the duplex ultrasound measure, that is, PSVR with angiography. In fact, the literature supports a PSVR of greater than or equal to 2.5, indicating greater than or equal to 50% angiographic stenosis.

Now I will discuss the primary efficacy endpoint results.

This chart shows evaluable data for the efficacy endpoint, and it breaks down missing data by reason. The percent of patients excluded from the primary patency endpoint was similar between groups, with 16.5% in the Lutonix DCB arm and 15.6% in the standard PTA arm. Overall, 83.5% in the Lutonix DCB arm and 84.4% in the PTA arm were evaluable for primary efficacy.

I would like to call your attention to the fact that the number of actual duplex ultrasound exams that could not be interpreted was impressively low at 6% in the Lutonix DCB arm and 5.6% in the standard PTA arm.

Here you will see the primary patency results. The primary

efficacy endpoint at 12 months was achieved, showing superiority for Lutonix DCB at 65.2% to that of standard PTA at 52.6%, an absolute difference of 12.6% between the groups. Additionally, after adjusting for prespecified covariates, the treatment effect was robust with a p-value of 0.015.

This is the Kaplan-Meier survival analysis of primary patency. At six months, the lines separate at the time of follow-up ultrasound. This time-to-event analysis showed superior patency in the Lutonix DCB group, and the difference is sustained through 12 months. The difference between arms at 12 months was significant, with a log-rank p-value of less than 0.001.

In an effort to better understand the relationship of duplex ultrasound findings with clinically meaningful endpoints, we evaluated our duplex ultrasound results for the entire cohort and compared them to TLR and Rutherford class.

Table 1 shows the percentage of patients with core lab-adjudicated restenosis at six months, who subsequently had a target lesion revascularization through the 12-month follow-up window. Patients who were patent at six months by duplex ultrasonography were statistically unlikely to require revascularization.

Table 2 shows that the clinical symptoms, as evidenced by Rutherford class, were better for patients who had patent target lesions by duplex ultrasound than for those who had a stenosis. Notably, based on the median Rutherford score of zero, more than 50% of patients had unlimited

walking ability when their ultrasound demonstrated patency. I am unaware of similar correlations in femoropopliteal device studies to date.

Let us move on to the supportive analyses. Generally, supportive analyses are designed to identify trends. These are typically underpowered. The subgroup analysis also may not have the protection of balance from randomization. The usual outcome is that the results trend in the same direction as the primary endpoint.

This forest plot shows the difference in primary patency by prespecified subgroup, with data points to the right of zero indicating efficacy favoring Lutonix DCB. Though the study wasn't powered to show differences in any of these subgroups, the treatment effect for primary patency generally favored Lutonix DCB across most subgroups and is encouraging. The wide confidence interval for the SFA and popliteal subgroup was due to only three patients in that subgroup.

Some variation was noted with geography and the p-value for interaction by geography was 0.122, suggesting the possibility of an interaction.

There was also variation observed with gender. Females had less evidence of a positive treatment effect with the Lutonix DCB, though this was not a prespecified interaction test.

When we explore gender and geography further, we see consistent results in males, regardless of geography, and the same effect for

females in the European Union. The U.S. female subgroup is a clear outlier. It's difficult to conclude from these data that the Lutonix DCB is less effective in subgroups based on either gender or geography alone.

To further understand these results, we looked at various effect modifiers. Based on exploratory analyses, these variations appear to be largely explained by other factors and interactions. As you will hear in the interaction discussion, the treatment by geography and treatment by gender interaction is highly dependent on smoking. Thus, accounting for an imbalance in smoking between the geographies and gender mitigates concerns about poolability.

I will now walk you through the per-protocol results for efficacy.

The Sponsor prespecified, in their statistical analysis plan prior to unblinding, a per-protocol analysis. Patients included in the per-protocol analysis were ITT patients that did not have one of the listed protocol deviations shown here. As you can see in this slide, exclusion by core lab determined geographic miss for the per-protocol analysis created a significant imbalance in groups, with 7.6% of patients included in the DCB arm and almost 22% of patients excluded in the PTA arm. This calls into question the validity of the analysis. Geographic miss led to loss of balance afforded to the data through randomization, which was only discovered after unblinding.

As previously presented, the prespecified primary analysis was

based on the ITT population and demonstrated superiority in primary patency. The prespecified per-protocol analysis was performed, though flawed by the geographic miss definition and resulting imbalance. The result from that analysis demonstrated primary patency rates of 65.3% and 56% for the Lutonix DCB and control groups, respectively. The difference was 9.3% in favor of the DCB treatment, with a corresponding p-value of 0.107. Note that because of the smaller sample size for this analysis, power for the treatment effect was lost relative to the primary analysis.

In an attempt to address the issues in this analysis, the Sponsor performed an alternative post hoc per-protocol analysis, in which the geographic miss patients were not excluded from the population that met entry criteria. This analysis provides a more balanced population between treatment arms and is more reflective of standard per-protocol analyses. And superiority of DCB patency is consistent with the primary analysis.

Finally, I will review the secondary endpoints.

Here is a summary of secondary endpoints at 12 months. There were two sets of prespecified analyses for secondary endpoints. The first had a hypothesis test which included target lesion revascularization, target vessel revascularization, and composite safety events at 12 months.

There were numerous other secondary endpoints that were analyzed with descriptive statistics. None of these secondary endpoints were expected to show a significant difference. The trends favor the Lutonix DCB

and are encouraging.

Change in Rutherford classification and the walking distance component of the Walking Impairment Questionnaire indicate improved physical functioning of patients. These are key functional outcomes, which were sustained over 12 months.

87.7% freedom from re-intervention at 12 months, shown here, is an excellent and meaningful clinical result. Though this result is numerically favorable for DCB, it was not statistically superior. The numerical separation of TLR between the Lutonix DCB and standard PTA begins between 6 and 12 months.

The lack of a statistically significant difference between treatment and control is a bit surprising. But as Dr. Rosenfield mentioned earlier, there were unique aspects of this study design that could have impacted this clinical decision. These include the blinding of the clinician at each follow-up through the 12-month window, along with blinding to the duplex ultrasound results. This blinding strategy likely led to less intervention in the control arm compared to other studies. Also, bailout stenting was not considered a TLR.

As a reminder, this study was not designed to show difference in any of the secondary endpoints.

The blinding strategy did appear to effectively control much of the bias in other studies. Here you see that both Lutonix DCB and standard

PTA groups had the same rate of re-interventions among patients with patency failure.

Furthermore, we looked at the patients without improved clinical status. In this subset, the rate of TLR for the DCB and control groups was comparable. This shows lack of bias in the subjective clinical decision to re-intervene.

Now, let me discuss several clinically relevant analyses among the various secondary measurements tested in this study. We wanted to assess trends and outcomes of these measures, even though the study was not powered to do so and they are not adjusted for multiplicity.

The Walking Impairment Questionnaire is a validated tool to measure physical function in patients with peripheral artery disease. The Walking Impairment Questionnaire is comprised of several different measures and analyses.

Patients in this study were enrolled because of claudication. In this assessment, the patient answers a question about the degree of difficulty in walking up to five blocks. Specifically, the question asks the patients to report the degree of physical difficulty that best describes how hard it was for you to walk on level ground without stopping to rest for each of the distances shown here. A higher number suggests that the patient can walk farther without discomfort.

One of the components of the Walking Impairment

Questionnaire, the WIQ walking distance, showed a statistical difference between DCB and PTA. Consistent with the primary patency analysis, the assessment of walking distance demonstrates an improvement at 12 months compared to baseline. There was a larger change in the Lutonix DCB group, as seen here in blue, as compared to the standard PTA group, shown in green. This difference was statistically significant at a p-value equal to 0.017.

Next, I would like to show you improvement in Rutherford class. As a reminder, eligible patients in this study were class 2 to class 4, which suggests that these patients had moderate to severe claudication or ischemic rest pain.

To put these classifications into perspective, in my practice, when I assess a patient's clinical symptoms and they tell me they can't walk a block, about 80 meters, without pain, then I will routinely classify them as class 3.

The second clinically meaningful measure we assessed was the benefit for patients based on Rutherford class. This Kaplan-Meier analysis compared the Rutherford class at baseline to the Rutherford class the patient had during follow-up. If a patient exhibited the same or worse Rutherford class at baseline, they were considered failures. Patients in the DCB arm had a sustained improvement in their clinical outcomes more often than patients treated with PTA, with 82.7% in the DCB arm compared to 73.4% in the PTA arm, with a p-value of 0.027.

In addition, we performed a post hoc Kaplan-Meier analysis of improvement in Rutherford class without target vessel revascularization. Patients treated with a DCB had a sustained improvement in their clinical outcomes more often than patients treated with PTA at 12 months, with a difference of about 10% and with a p-value of 0.041.

In regards to patency in longer lesions, this table shows a prespecified subgroup analysis for lesions > 14 cm. It appears from this data that the DCB has a reduction in patency for this subgroup. However, with only 23 patients, the sample size is too small to make any meaningful observations.

Another prespecified subgroup was an analysis by lesion length quartiles, each with approximately 100 patients. In this analysis, the longest lesion length quartile does retain the benefit of DCB over PTA.

As a caution, analyses by subgroups are very sensitive to specific cutoff thresholds.

Furthermore, when lesion length is considered as a continuous variable, the p-value for an interaction with treatment effect is 0.8. Since lesion length is not an effect modifier overall, conclusions from subsets determined by lesion length should be interpreted with caution.

To further understand the sustained treatment effect of DCB over standard PTA, we performed additional Kaplan-Meier analysis out to 24 months. However, the Sponsor was able to obtain this longer-term data on

less than half of the population. Since patients without prior failure are censored in this analysis at the time of last follow-up, only 26 versus 14 patients are at risk. Therefore, until more follow-up is available, each event results in a disproportionate drop in the curve. Although it appears that the overall patency rate drops for both arms, the benefit of the DCB, even in the light of this more limited longer-term follow-up, is sustained out to 24 months, with a log-rank p-value of 0.021.

Since the approach on the previous slide was very conservative, the Sponsor performed an additional post hoc analysis where non-exited subjects had their status imputed out to 24 months. I should note that this analysis has been discussed with the FDA, but that they have not yet had a chance to review it. These results further support the durable benefit and patency for the DCB arm over the control PTA arm.

To summarize, we set out to perform a trial to demonstrate that the Lutonix DCB would have superior patency at 12 months over PTA. The LEVANT 2 trial proved that point. In LEVANT 2, the primary patency endpoint was met and the data demonstrated clinical benefit to the patients treated with the DCB. The Lutonix DCB had a 12.6% greater patency at 12 months over standard PTA and the result was statistically significant at a p-value of 0.015.

Supportive and subgroup analyses results were generally consistent with the primary endpoint analysis.

Also all patient-reported outcomes were consistently in favor of the Lutonix DCB, and the trends look encouraging.

Although these analyses were not adjusted for multiplicity, we saw significant improvement in the walking distance portion of the WIQ, suggesting that patients do walk farther without discomfort.

Additionally, we saw a significant improvement in Rutherford class between DCB and PTA arms. We did not see a difference in TLR, though we saw sustained improvement in Rutherford class in patients who did not require a re-intervention.

Thank you. I will now turn the presentation over to Dr. Ansel to review the safety data.

DR. ANSEL: Thank you, Dr. Jaff.

Good morning. My name is Gary Ansel, and I am the System Medical Chief for Vascular Services at Ohio Health/Riverside Methodist Hospital, and an Assistant Clinical Professor of Medicine in the Department of Internal Medicine at the University of Toledo. I am a founding board member of the Vascular Interventional Advances Conference, called VIVA, and am a former member of the peripheral vascular committee for the American College of Cardiology.

The primary safety endpoint at 12 months included freedom from all-cause index limb re-intervention, all index limb amputations, including both major and minor amputations below the ankle, index limb-

related death, and all-cause perioperative death. This was a non-inferiority analysis with a 5% margin.

Here you see a flow diagram for evaluable safety data broken down by missing data by reason. The percent of patients excluded from the safety endpoint was similar between both groups, with 9.5% in the Lutonix DCB arm and 10.6% in the standard PTA arm. Overall, 90.5% of Lutonix DCB patients and 89.4% of PTA patients were evaluable for primary safety analysis.

Let's now look at the results. The primary safety endpoint was met. The proportion of patients free from any safety event in the Lutonix DCB arm was 83.9% compared to 79.0% in the control group at 12 months. The study demonstrated non-inferiority with a p-value of 0.005.

Here we break down the safety events by treatment group. There were no perioperative or index limb-related deaths in either the Lutonix DCB or standard PTA group. There was a single amputation in the DCB group. Overall, the safety endpoint was driven by fewer limb-related re-interventions in the Lutonix DCB group compared to the standard PTA group.

We also looked at the primary safety endpoint using a Kaplan-Meier survival analysis. At 12 months the curves overlap, showing no evidence of statistical difference between the groups and further confirms non-inferiority.

We also looked at safety by subgroups. This plot shows the safety/risk difference by lesion subgroup. The risk estimates to the right of zero favor Lutonix DCB compared to risk estimates to the left, which favor PTA. Please remember that these safety comparisons, by design, are based on non-inferiority. The p-values reflect subgroup interactions.

Bailout stenting status, chronic total occlusion, lesion length, and lesion location show consistent non-inferiority of Lutonix DCB compared to standard PTA. The confidence interval for the SFA popliteal group is largely due to the subgroup containing only three patients. Similarly, there are 35 subjects in the popliteal subgroup.

As a reminder, supportive analyses are underpowered and frequently have comparisons that do not have the protection of the balance from randomization.

This plot shows gender and geography subgroups. There was also consistent non-inferiority of DCB compared to PTA in that the point estimates for the differences were close to zero or favor Lutonix DCB. However, there was significant evidence of interaction by geography, with a p-value of 0.021.

We further explored this interaction. It appears that geography differences are significantly driven by gender, with dramatically favorable results for European females, based on 50 patients. These favorable results were driven by comparatively poor results for female European PTA patients.

Results for other gender/geography combinations show differences closer to zero, consistent with non-inferiority.

Again, this additional supportive analysis did not have the protection of balance from randomization and are informative but are difficult to draw conclusions from the data.

As a reminder, the primary analysis was performed on the ITT cohort, with non-inferiority demonstrated, and all patients in the study, post-randomization, received their assigned treatment. Therefore, the ITT results and as-treated results are the same.

As was prespecified, safety was also analyzed using the per-protocol population. As discussed earlier, this analysis was flawed by the inclusion of core lab determined geographic miss that led to a significant imbalance in exclusions. Additionally, there was a loss of power due to small sample size.

Similar to what was done for the primary efficacy endpoint, the Sponsor conducted an alternative per-protocol analysis in which the geographic miss patients were not excluded from the population that met entry criteria. The post hoc per-protocol and the ITT/AT analyses provide similar safety results.

Now, turning to secondary safety endpoints, no statistical differences existed in any of these secondary endpoints at 12 months, and the numerical differences were small. It is important to note that there were

no differences in death, major amputations, thrombosis, or major vascular complications.

Now, focusing specifically on the deaths at 12 months, the death rate was comparable between the two study arms, with 2.4% in the Lutonix DCB arm and 2.8% in the standard PTA arm; no deaths adjudicated by the CEC as related to the device, procedure, or index limb.

In the Lutonix DCB arm, the deaths were due to cancer, cardiac arrest, and ischemic stroke. There were four patients whose cause of death was unknown but for this analysis are conservatively categorized as cardiovascular deaths.

In the standard PTA patients, two patients died of cancer and one died from an intraoperative myocardial infarction during a procedure unrelated to the study. There was one PTA patient in which the cause of death was unknown and also categorized as cardiovascular death.

I'd like to now walk you through the adverse events in greater detail.

This table shows serious adverse events that occurred in 2% or more of patients. As expected in a patient population with peripheral arterial disease and associated comorbidities, approximately 50% of subjects in each treatment group experienced at least one serious adverse event during the study. The most common adverse events were claudication and restenosis of a non-study vessel.

We wanted to look further at angina and stroke, as they appear to be different between the two groups and are of particular interest with respect to safety.

As you can see, none of these events were adjudicated by the CEC to be either device, procedure, or drug related. Furthermore, the average time to event was 250 days for angina and 162 days for stroke. These rates are similar to the rates found in the symptomatic PAD cohort of the previously mentioned REACH study, where admission for unstable angina was 4.5% and non-fatal stroke was 1.9%.

All CEC-adjudicated events that were probably or highly probably related to the device are shown here. As a reminder, the CEC was blinded to the patient's randomization assignment

Device-related serious adverse events were reported in 10.8% of Lutonix DCB patients and 16.9% of standard PTA patients. Individual events occurred with similar frequencies in the two treatment groups. The most common were claudication and target vessel injury or dissection, which were both numerically higher in the standard PTA arm compared to the Lutonix DCB arm. Additionally, there were unanticipated adverse device effects.

Now, looking at procedure-related serious adverse events, overall, procedure-related adverse events were reported somewhat more frequently in the standard PTA arm, with 20% of PTA patients compared to

14.9% of Lutonix DCB patients. Procedure-related vessel injury and claudication were numerically more common for standard PTA.

To supplement the primary safety analysis, we also looked at the interim safety data through 24 months. As previously mentioned, at 365 days, 86.7% of Lutonix DCB patients and 81.5% of standard PTA patients were free from safety events. To more fully evaluate long-term effects, we were able to evaluate 24-month data on a limited number of patients. At 730 days the lines widen slightly, with 80.6% of Lutonix DCB patients free from events, compared to 72.6% in the standard PTA group. Including interim 24-month data, the results continue to demonstrate non-inferiority with a p-value of 0.022.

Looking closer at the serious adverse events through 24 months, we continue to see comparable percentages between groups for overall serious adverse events, both device- and procedure-related events as well as for deaths.

In addition to the patients enrolled in LEVANT 2, there was a LEVANT 2 safety registry, agreed upon with FDA, to monitor additional Lutonix DCB patients. The registry used the same enrollment criteria and follow-up schedule out to five years. This single-arm registry enrolled 657 patients and completed enrollment in September of 2013, and all events are being collected and adjudicated by the CEC.

The Sponsor also continued to look for rare adverse events

through the LEVANT 2 randomized and safety registry studies. In discussions with FDA regarding the design of the LEVANT 2 safety registry, it was recommended that the Sponsor collect sufficient data to detect unanticipated device- or drug-related adverse events at a 95% confidence interval upper bound of 1.8%. As prespecified, Lutonix pooled all DCB data from LEVANT 2 randomized, including roll-ins and the LEVANT 2 safety registry, to achieve the minimally required sample size of 869 patients.

A total of 1,029 DCB patients were enrolled between the two studies. We have seen no unanticipated adverse events to date. Our upper bound 95% confidence intervals are listed here. From this we conclude that the rate of unanticipated adverse events is less than or equal to 0.69% at 12 months at the 95% confidence level, which is less than the 1.8% prespecified detection rate for the safety evaluation. For example, the target vessel thrombosis we observed a rate of 0.18% with a 95% confidence interval upper bound of 0.99% through one year, which is far below the prespecified 1.8%.

In summary, the primary safety endpoint was met and there were comparable adverse events observed between the Lutonix DCB and standard PTA arms. There were no deaths related to either the procedure or device, and there were no unanticipated adverse device effects.

Finally, when looking at long-term data from our interim 24-month analysis, we saw similar events in both the Lutonix DCB and

standard PTA groups, suggesting no increased risk with the Lutonix DCB.

Chris Mullin will now review interactions.

MR. MULLIN: Good morning. My name is Chris Mullin. I am a statistician with NAMSA.

Drs. Jaff and Ansel described the results for safety and efficacy by gender and geography. I will be discussing these findings in more detail.

While it is common in clinical trials to examine subgroups, these analyses are generally considered exploratory and hypothesis generating, as there may be substantial statistical limitations. Such analyses, by definition, focus on subgroups which have smaller sample size and an increased chance of imbalance and confounders. There is also a potential for false positive findings. As such, it is difficult to draw definitive conclusions from such analyses.

Let me describe the methods we used for this analysis. For the set of 12 prespecified covariates, we determined whether there were other statistically significant treatment by subgroup interactions. The goal was to see if another factor might be driving the gender or geography differences. In doing this, we identified smoking status as a potential effect modifier for the efficacy endpoint, with a p-value of 0.001. The only other potential effect modifier was gender, with a p-value of 0.013, which was discussed previously. We also noted that smoking varied significantly by both gender and geography.

Since the FDA noted a significant three-way interaction between gender, geography, and treatment and we identified smoking as another important factor, we took the next step of exploring the four-way interaction of smoking, gender, geography, and treatment. The p-value for this four-way interaction is 0.09.

This figure displays the treatment differences for the eight subgroups defined by gender, geography, and smoking. For seven of the eight subgroups, the treatment difference favors the Lutonix drug-coated balloon with differences between 8.4% and 40.7%. Only in the U.S. female non-smokers does the treatment difference favor standard PTA.

So we looked further at the U.S. female non-smokers. For non-smoking U.S. females, we identified a number of baseline and procedural characteristics that differed between the randomized groups. This included significant differences for reference vessel diameter, dissections, bailout stenting, and minimum lumen diameter post-treatment. While these factors do not completely explain the variation in treatment effect in this subset, there are likely other imbalances, including unmeasured factors that exist that may have led to the result. These observations are interesting and will be evaluated further post-approval.

Now, for safety. We used the same methodology to explore results by gender and geography. Here we did not find any significant effect modifiers amongst the 12 prespecified covariates. The smallest p-value was

0.30.

This forest plot shows the results for safety by gender and geography. The blue circle near the bottom of the slide shows that in females in Europe, the PTA control group had a freedom from safety event rate of 44%. This is in contrast with the other subgroups, defined by gender and geography, that generally have safety results consistent with non-inferiority with rates of around 80%, ranging from 75% to 94%. Again, sample sizes for these subgroups are small. The outlier subgroup of control EU female patients had a sample size of 16. While the interaction is largely driven by this one subset of PTA subjects, the overall results do provide reasonable evidence of safety for the Lutonix DCB.

To summarize, in post hoc exploratory analyses, we go deeper into the questions of gender and geography by treatment. For efficacy, we discovered another factor, smoking, that plays a strong role in the gender/geography differences. For safety, we did not find any such significant effect modifiers.

Again, we consider these analyses exploratory and hypothesis generating with need for further study. Thus, we believe the findings of these interactions are interesting but do not modify the overall primary patency and overall safety conclusions.

Thank you. John DeFord will now discuss post-approval.

DR. DeFORD: We're committed to the ongoing safety

monitoring of patients with the Lutonix drug-coated balloon. We have proposed a postmarket strategy to continue to gather long-term data on safety and efficacy.

The post-approval cohort will include 1,029 Lutonix DCB patients followed out to five years. From LEVANT 2, we'll continue to follow 372 randomized and roll-in DCB patients as well as 657 LEVANT 2 safety registry patients, including 238 additional females.

We will conduct hypothesis tests for efficacy and safety on the post-approval study dataset.

For efficacy, we will analyze for superior primary patency of all LEVANT 2 Lutonix DCB patients versus LEVANT 2 control PTA patients at 24 months.

For safety, we will analyze for non-inferiority of freedom from composite safety at 12 months of LEVANT 2 safety registry Lutonix DCB patients versus LEVANT 2 control PTA patients.

In addition, we are enrolling up to 1,000 patients in a real-world global SFA registry to provide additional supportive information on efficacy and safety post-approval.

I'd now like to invite Dr. Mustapha to conclude with the benefit-risk assessment.

DR. MUSTAPHA: Thank you.

I'm Jihad Mustapha, Director of the Cardiovascular Cath

Laboratory and Clinical Assistant Professor of Medicine at Michigan State University.

As an interventional cardiologist, treating this disease is my daily battle. I'm constantly looking for new options to provide PAD patients relief for their pain and, more importantly, saving their limbs from amputations.

As you've heard, PAD affects a large number of once-active American patients. The typical symptomatic PAD patient experiences daily limitations. These include difficulty walking to the mailbox or in a grocery store or even simply getting a glass of water. This is their daily struggle.

But it doesn't stop here. PAD is a progressive disease. It can cause critical limb ischemia, characterized by pain at rest, and can lead to amputation. A disease can progress into advanced stages which are associated with high mortality rates due to cardiovascular events that is sixfold greater in patients with PAD. In fact, PAD causes a higher mortality rate than many cancers.

My patients deserve a product that has any superiority to current angioplasty, which would further delay or halt disease progression. Let me give you an example of the type of patient who would benefit from this technology.

Stenting is not the best option for this patient, and many of us try to avoid stenting for these patients at all costs. Evidence shows that

stents in these areas often occlude, leading to repeat procedures and, as shown here, have high fracture rates in the SFA and popliteal.

I just saw a patient with a blockage starting behind the knee and had a life-limiting claudication and who is typical of many of the patients that we see on a daily basis. We struggled on the best way to treat this individual because of the challenging anatomical location and composition of the disease. But then I'm left with no treatment options other than standard PTA. This has been the case for over 15 years. This is a perfect example of a patient where the Lutonix DCB would not only be a valuable tool, but will be the only tool available.

This technology will help add significant value to an area of medicine with significant unmet need. It is a simple but innovative idea: adding a proven drug to a proven device to improve clinical patency. Of course, simplicity does not justify sacrificing efficacy or safety, which is what the LEVANT 2 trial was designed to assess.

The LEVANT 2 study provided Level 1 evidence of non-inferior safety to standard of care PTA. The study showed similar adverse event rates between groups. There were no deaths related to either procedure or device, and there were no unanticipated adverse device effects. Additionally, no negative safety signals were observed with interim 24-month analysis. The LEVANT 2 also provides Level 1 evidence of superior efficacy over the standard PTA.

The intended role of the Lutonix DCB is to restore patency in native stenotic or occluded femoropopliteal arteries for patients suffering from claudication or ischemic rest pain. Clinically, this means relief of symptoms for the PAD patient. This is commonly measured in practice by change in Rutherford classification and walking improvement. These measures translate to patients being able to walk their dog and play with their grandchildren again. These may sound like simple tasks, but for many of our patients, completing these tasks allow them to regain lost independence.

We are currently in need of a new safe and effective non-implantable therapeutic option. The Lutonix drug-coated balloon enables us to treat our patients without limiting future treatment options, a limitation often associated with stenting. The Lutonix drug-coated balloon shows clinical benefits with an acceptable safety profile compared to standard PTA.

Based on the totality of evidence, I am confident that physicians in the United States should have the option to offer a drug-coated balloon to the rapidly growing PAD patient population, just as our peers have in Europe since 2008, where in many institutions a drug-coated balloon has become the first line of treatment.

The data presented today from the randomized multicenter trial provides a reasonable assurance of the safety and effectiveness of the Lutonix drug-coated balloon.

Thank you very much. John DeFord will return to take your questions.

DR. PAGE: Is that it?

DR. DeFORD: Yes.

DR. PAGE: I want to thank you for a concise and clear presentation. I really appreciate you and all the speakers.

We have a further Panelist who's on the line, Dr. Magnus Ohman.

Dr. Ohman, can you hear us?

DR. OHMAN: Yes, Dr. Page, I've been hearing it very well.

DR. PAGE: Beautiful. And we can hear you very well also. If we neglect to call on you, when appropriate, please speak up and I'll try to keep in mind that you're on the phone. And I understand that this isn't by your own doing that you're not with us today, so I'm sorry for your difficulties in travel.

DR. OHMAN: Thank you.

DR. ZUCKERMAN: Good morning, Dr. Ohman. For the record, can you identify your affiliation, please?

DR. OHMAN: Yes. My name is Dr. Magnus Ohman. I am an interventional cardiologist at Duke University Medical Center in Durham, North Carolina, that is only served by commuter airlines.

(Laughter.)

DR. PAGE: Thank you, Dr. Ohman.

It's now time for the Panel to ask any brief clarifying questions of the Sponsor. Keep in mind, we will have time to ask the Sponsor questions during the Panel deliberations in the afternoon.

Dr. Somberg.

DR. SOMBERG: Yes. I wonder if you can clarify -- maybe the first presenter of the day -- the sequence in clinical practice, because I seem to get the impression that you're saying, in this geographic area, you eschew stenting, but then I heard, if it fails, you do stenting. And if you're doing stenting and this comparative trial is to balloon, do you have -- and this is my follow-up question -- do you have comparative data on this device with obviously not a controlled study, but with outcomes with stenting and how that compares? Because it seems to me that there's a clinical decision-making tree that physicians have to go along, and we're really giving only part of the database for the decision making to be made, of comparing to balloon and not comparing to balloon and stent.

DR. DeFORD: Okay, thank you. Just to make sure, I heard two questions in there. The first question was the standard of care today and whether this was the right comparator. And the second question is, do we have data with stents to be able to share today?

So, in the first question, to answer that question, we could ask a clinician to come up. I'll try to answer this briefly, and if that's not

sufficient, we'll ask a clinician.

But standard of care today is provisional stenting, that is, PTA alone, and if PTA fails, stent. That's actually what we did in this study. We had the pre-dilatation, which was in an attempt to isolate those patients that were destined to have a bad outcome with PTA and then isolate them so that we could compare the drug effect without the interaction of a stent, which is known to have some patency benefit as well.

The second part of your question, do we have data with stents, we only have the very small amount of data in the bailout stent population. So we had 8 versus 11. Other than that, we don't have additional details.

DR. SOMBERG: May I --

DR. PAGE: Your microphone was left on, anyway. So, yes, please follow up. You're off now. It's difficult for the Panelists to see whether the light is on or not.

DR. SOMBERG: Oh, you can't -- I'm sorry.

DR. PAGE: It's not visible to the Panelists.

DR. SOMBERG: I will now keep my head in this position.

(Laughter.)

DR. PAGE: There you go. Thank you.

DR. SOMBERG: Okay. Well, I understand that you're saying that initially you do a pre-dilation. And maybe it would be good for the clinicians to come up and answer this, too, but you do a pre-dilation. But

over the time course of the patient's care, if there is failure or not a good improvement or recrudescence of symptoms, I understand that many people will go in and put a stent in. Therefore, I think it might be useful, over maybe the lunch break or something, to take the historic database with stenting and present patency and improvement in function -- there are historic records -- and compare it to what you're presenting with the DCB.

DR. DeFORD: Okay, we can try to do that. I want to remind you that the purpose of the study was to evaluate a technology that didn't require a stent, leaving the opportunity for additional treatments in the future for these patients, which could include stenting. And so that was the primary purpose of the study, improve PTA without requiring a stent.

DR. PAGE: Maybe if I can clarify. And, Dr. Somberg, tell me if I've gotten this right. Your question is, for the patients who did undergo stenting down the line, for clinical indications, how did they do with the drug-coated balloon versus the standard PTA, in terms of after they underwent a stent? Is that your question?

DR. SOMBERG: Well, that's a permutation of it, and that's a very interesting comparator, too. But I'm interested in understanding practice today, which I understand is, well, you don't like to do a stent in that area, but they still do a stent in that area, and how that compares to now using the DCB.

And so there's a historic experiential database, and then we

have the LEVANT 2 trial and even the LEVANT 1 plus 2 trials, and you could make a comparison there because I see that there is efficacy with balloon. In terms of patency, there's a little additional efficacy -- and we'll discuss that today -- with the drug-eluting balloon. But how that fits into the current standard of practice is really not described. And while we are offering -- while the Sponsor is asking for approval of an additional tool, we have to put that into the context of the myriad of interventions available in this area.

DR. DeFORD: Dr. Page, if we have just a moment, I can show a slide that does compare to primary patency and TLR, of this technology, to a number of the stent technologies.

DR. PAGE: Okay, go ahead, please.

DR. DeFORD: And so if I direct you to the screen, you can see that our primary patency is comparable at 65.2%. You can see RESILIENT, which is a LifeStent device, at 81%. Zilver PTX, DURABILITY II, another device, and so on. You can see that we're in the range of primary patency without a stent and also similar re-intervention rates compared to stents.

DR. PAGE: Dr. Somberg, did that -- and I want to move on to other questions. But if there's a specific analysis that you're requesting or needing perhaps after lunch, is that what you're driving at?

DR. SOMBERG: Well, that one is very helpful.

DR. PAGE: I'm sorry?

DR. SOMBERG: I just wanted to say that's very helpful. If they

had something with functionality, too, that would also be useful.

DR. PAGE: Okay.

DR. ZUCKERMAN: And let me add one additional point. If you can give us, after lunch, a little bit more background on the patient populations in those studies so we can better understand comparability of the 12-month results.

DR. DeFORD: Certainly. We have that information we could provide now. If you'd like to wait until after lunch, that's fine. Okay.

DR. ZUCKERMAN: After lunch.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: Thank you.

Two questions. When I look back at the sensitivity of Doppler ultrasound to identify patients, that 2007 paper indicated a moderate sensitivity, and that is 81% for detecting stenoses greater than 50% with a positive predictive value of 0.84 and a negative predictive value of 0.91. When one looks at the primary efficacy endpoint here, did the statistics in terms of the power calculations account for that delta is my first question.

DR. DeFORD: The power calculation did not specifically take that into account.

DR. CIGARROA: The second question is, in looking at the definition of primary patency, the definition was peak systolic velocity ratio of greater than 2.5 and freedom from target lesion revascularization. If I look at

prior studies such as Zilver PTX, there was a difference in the threshold for defining a stenosis of greater than 50% and that used a ratio of two from the same core lab, and I wanted a little bit of clarification of why that difference. And that particular trial did not include both the Doppler finding and freedom from target lesion revascularization. So could you clarify the differences in the ratios used?

DR. DeFORD: Yes. I'd like to ask Dr. Jaff to come and speak to the variations here.

DR. JAFF: Thank you. Michael Jaff.

You're right. In Zilver PTX, the trial that started before this trial, the data that was in the literature largely was supported by a peak systolic velocity ratio of 2.0 or greater. Subsequent to that, a number of studies had suggested that a better predictor of correlation with greater than 50% angiographic restenosis was greater than or equal to 2.5. So that's the reason that there was a difference in the ratio.

DR. CIGARROA: Thank you.

DR. ZUCKERMAN: Dr. Jaff, could I ask you one more question? I believe the Sponsor has done several analyses that show that the exact value in that range isn't really important for showing what you want to show, and maybe you can show that after lunch, that it's a robust result.

DR. JAFF: Yes, thank you.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: A final follow-up is would it be possible to present data after lunch, looking at the isolated endpoint of the Doppler data and the target lesion revascularization?

DR. DeFORD: Yes.

DR. CIGARROA: Thank you.

DR. DeFORD: We have that information.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Simon.

DR. SIMON: Sure. Can you just help me reconcile one point? And I'm working off the FDA document. On your inclusion criteria, subpoint 6 was at least one -- and I'm just going to read -- one patent native outflow artery of the ankle free from significant (> 50%) stenosis.

If we go to Table 10 -- and I'm not expecting you to have that in front of you, but for the benefit of the group there are, I think, 30 patients in -- 9.5% of the patients in the DCB group have no patent runoff vessels. It's Table 10. You have 30 in the DCB with no patent runoff vessels and 13% in the control with no patent runoff vessels. So I'm just wondering how you reconcile that group of patients with your inclusion criteria.

DR. DeFORD: Let me just pull that up. We have it here.

DR. SIMON: Sure. It's Table 10. I'm just working off the --

DR. PAGE: Do you have the page in the Sponsor Panel Pack?

DR. SIMON: The Sponsor panel is page 27, but that's --

DR. DeFORD: Yeah, that's a little busier. There was a previous slide, but certainly we have this here, and you can see that we did have roughly 10% of patients with no runoff. And that's correct, although this was --

DR. SIMON: Sorry. I mean, how are those patients included, then?

DR. DeFORD: That would be a protocol violation to have included those patients. Again, this is determined -- the determination was by -- the investigator, at the time, thought that they had patent runoff vessel, and then in subsequent analysis, we find that they don't.

DR. SIMON: Okay.

DR. DeFORD: But yes.

DR. SIMON: And just as a follow-up, you know, in reading through the materials, I was -- I appreciate Dr. Rosenfield's explanation of a geographic miss. It was a concern. But this point then. The data was never run -- am I correct in saying that the data was never run with these patients and then excluded from the analysis?

DR. DeFORD: That's correct.

DR. SIMON: Okay.

DR. DeFORD: Although we do have results by runoff vessel --

DR. SIMON: Okay.

DR. DeFORD: -- if you'd like to see that.

DR. SIMON: Sure. I mean, if we could see it after lunch, that would be fine.

DR. DeFORD: Okay.

DR. SIMON: I think we'll have a busy after lunch.

Thank you.

DR. PAGE: So just so I'm clear, you're asking the Sponsor if they could perform an analysis for the primary endpoint, eliminating the individuals who essentially, post hoc, were identified as violating the inclusion criteria but not having the patent runoff vessel.

DR. SIMON: Right, this is -- I mean, it just struck me, in reading through it, that this is a violation of their own inclusion criteria, and it's actually not a small -- it's 10% of the DCB patients. It's not actually insignificant. And so it may in the end -- I have to tell you I'm editorializing here. Actually, now that I hear Dr. Rosenfield's explanation of the geographic miss, I almost want to discard it, that is, this whole geographic miss analysis. I can say it's actually --

DR. PAGE: And we will have opportunity to discuss that at some length.

DR. SIMON: But this I would just want to see explored because they violate their own inclusion criteria.

DR. PAGE: So is that request clear to you?

DR. DeFORD: Yes. I put it on the screen, but we'll discuss it

after lunch. We did have the information, and I had thrown it up on the screen, but we can discuss it after lunch.

DR. PAGE: Great, thank you.

Dr. Gravereaux.

DR. GRAVEREAUX: Ed Gravereaux from Boston.

A quick clarification for the geographic miss concept. The pre-dilatation was with a balloon purposefully sized under, if I'm correct, what the nominal vessel was.

DR. DeFORD: Yes, it was to be sized 1 mm roughly less than --

DR. PAGE: By "under" you're talking diameter and not length; is that correct?

DR. GRAVEREAUX: Diameter, correct. So from a standpoint, then, why would that impact the then un-subsequently treated vessel if it's undersized? So I think the concern would be barotrauma or extra barotrauma to that portion of vessel, which would then not subsequently have drug-coated balloon exposure, correct?

DR. DeFORD: That's correct.

DR. GRAVEREAUX: So, then again, does that become important if it's an undersized balloon, without resultant barotrauma to that little pre-dilated segment?

DR. DeFORD: Yes. And so just to clarify. With the drug-coated balloon, if we had, just as you described, pre-dilatation -- even though it was

less than 1 mm, if you have pre-dilatation and you didn't completely cover that with the treatment balloon -- drug-coated balloon -- you would have a geographic miss; you would not deliver drug.

On the other hand, if you were using standard PTA, if you induced an injury, that was standard PTA. To go back and reinflate it again if you had a good result didn't really do anything. And so that was the confusion that we had when we really honestly had not taken -- carefully considered the impact of geographic miss in the control arm.

DR. PAGE: And I would point out that we will have an opportunity to discuss the issue of geographic miss after lunch.

Dr. Posner.

DR. POSNER: Thank you.

I have two questions. Have you done any pharmacokinetics analyses on the drug delivery and the drug staying power? In other words, distribution throughout the rest of the vessel and how long it actually does have an effect in place, other than your 12-month longitudinal study.

DR. DeFORD: Yes, we've certainly done animal studies where we placed the device, inflated the balloon, and then measured at multiple time points, and we found sufficient drug beyond -- at 30 days. In fact, I can show you this. It's a little messy, but I can show you that because the scale -- you can see that at 30 days and even 60 days, we have significant drug quantity in tissue to be effective, based on previous studies that have

demonstrated effectiveness of paclitaxel.

DR. POSNER: And my other question is, in your sub-analysis of smokers versus non-smokers, are you actually measuring pack-years? Because the question I have as an old pulmonary person is whether you're talking about people that smoked and then quit, people who have just started smoking, or people who have smoked their entire lives. And so a pack-year analysis might be really useful, if you had done that.

DR. DeFORD: I don't believe we collected that information. We just collected their current smoking status, and then we also, over the course of the study, collected any change in smoking status. But I don't believe we collected that information, but I can verify over the lunch hour and see if we have that information.

DR. PAGE: Dr. Hirshfeld.

DR. HIRSHFELD: Thank you.

This is just really something to sort of prepare you for later discussions. In going through these data, what's most on my mind is to have a better feel for the absolute magnitude of the effect size that you demonstrated. And most of the material that you've shown us today is in ratios and percentage differences, which are often percentages of percentages. And so I think that as we get more deeply into this today, it would be helpful if you were well prepared to be able to tell us more about what the absolute magnitude of the effect size is and the durability of the

effect size is.

DR. DeFORD: Okay.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: In reviewing the material, I saw that a good number of your lesions -- I think it was 40% -- are shorter than maybe 4 cm and the DCB has a better -- it's stated that it has a better efficacy in shorter lesions than longer lesions. Could you break down -- do you have the data breaking down above a certain amount, like 14 cm below that and in terms of efficacy? Because maybe the overall pool is infused with real easy cases and that may be a false -- so I'd be curious to know the efficacy and the more severe lesions to get the balloon. And also if you have stent --

DR. DeFORD: Okay, let me just show you --

DR. PAGE: Dr. Somberg, were you not satisfied by this slide that was shown?

DR. DeFORD: And just to remind you, although it wasn't in the specific slide, when we did an analysis looking at an interaction by lesion length, we did not find an interaction and found a p-value at 0.8, the interaction p-value. And I'd just caution you, as we said earlier, making specific cutoffs can be very risky in doing these analyses.

DR. SOMBERG: I understand that. I'm just trying to -- so do you have the -- this is the greater. Then, where are the ones with less in that

balloon?

DR. DeFORD: So less than 30 mm is the Q-1 number, 30 to 52.

DR. SOMBERG: Oh, I see. Okay.

DR. DeFORD: And, again, this was broken down by quartile, roughly 100 patients in each group.

DR. SOMBERG: Why is there only 300 patients in this analysis when you have all together a much higher number?

DR. DeFORD: Sorry, let me put that right back up. Again, roughly 100 patients in each group. There were 476 patients randomized into the study, and when we take into account those patients that were lost to follow-up at the one-year or didn't have duplex ultrasound, this accounts for the difference.

DR. PAGE: I have a technical question. Actually two technical questions. The excipient includes -- you mentioned two other chemicals in addition to the paclitaxel. Are there other materials in the excipient?

DR. DeFORD: No. So there were two other materials that are used, and that is polysorbate and sorbitol. These are known for safety and have wide use in IVs. Now, there is methanol that's used in the initial mixing to solubilize everything. The methanol volatilizes over time, and we only have, after the coating is dried onto the balloon, polysorbate, sorbitol, and paclitaxel.

DR. PAGE: And that's it?

DR. DeFORD: And that's it.

DR. PAGE: Three chemicals in total?

DR. DeFORD: That's it.

DR. PAGE: Okay, great. And the other thing is the video, I thought, was very nice. And perhaps the clinicians can answer this. Does it represent reality in a single case, in terms of patients who have received the drug-coated balloon? And in that I saw a wire go down and I saw a drug-coated balloon go down, I saw it expand, and then the device removed. And was there ever a patient treated without pre-dilatation?

DR. DeFORD: No, every patient was treated with pre-dilatation.

DR. PAGE: Okay.

DR. DeFORD: I tried to explain that -- and I apologize -- at the discussion of the video. After preparation of the vessel, then the DCB was used.

DR. PAGE: And there was a very nice explanation of why, because in part the excipient and the like can be rubbed off and I don't know what happens to it. But, in fact, every patient studied received a pre-dilatation and we have no data -- no patient that has been reported here ever failed to have a pre-dilatation before using the drug-coated balloon; is that correct?

DR. DeFORD: That's correct. And maybe just to clarify something. In future labeling, assuming the product were to be approved,

we're certainly fine with pre-dilatation.

DR. PAGE: Well, I think you're going where I was going, and that is the indication. It seems to me that to fail to recommend that -- I'd be interested in the Panel's discussion, but I would just raise that concern, and I'm glad you acknowledge that issue.

DR. DeFORD: And we agree. We're fine with adding that recommendation.

DR. PAGE: Great.

Other questions from the Panel? Dr. Cigarroa and then Dr. Lange. And we're shooting to end in about three minutes.

DR. CIGARROA: The decision to proceed accordingly with pre-dilatation was to try and isolate the effect of the drug, not because you were concerned per se that the drug and the coating would come off the balloon going through a stenosis, right? I mean, trials have been performed in Europe -- the THUNDER trial -- which did not require pre-dilatation in proof of concept; is that correct?

DR. DeFORD: That's correct. And I'm glad you brought up that point. Thank you. We've done preclinical studies to evaluate the loss of drug through tortuous paths, through difficult paths, and through up to a three-minute flow time and find that because, of course, most of the drug is trapped within the balloon and it's folded, there's very little that you lose going through that process. And even out to three minutes we have more

than 70% of the drug on the balloon, which is certainly sufficient for drug delivery. So that is correct.

We also, frankly, in the global registry have about almost 250 patients enrolled without pre-dilatation. However, as Dr. Page noted, we don't have any data to show without pre-dilatation. We think vessel preparation is probably required, and we think it's important for a clinician to make that decision. And, frankly, we're fine with the recommendation of pre-dilatation, if that's what the Panel suggests.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: In the interest of time, I'm going to just ask you all to provide some data just clarifying stuff sometime after the break, and it will center around these four things.

One is what drove target lesion revascularization, since that was one of the endpoints.

The second is just to -- in the proposed indications, it's for de novo lesions and restenotic lesions. So if you could tell us what percentage of lesions were treated in the study.

The third is this geographic miss is becoming an important issue. And just for clarification, Dr. Rosenfield showed a great example of geographic miss in a normal vessel, and if you have the data to say, in the PTA-treated group, how often was reference vessel normal, that on either

side you had a normal reference vessel as opposed to disease.

Two other things. One is I just want to clarify that the walking distance was actually self-reported and not measured.

DR. DeFORD: That is correct.

DR. LANGE: Okay.

DR. DeFORD: We did actually collect walking distance as well, and it trended in favor of the drug-coated balloon, but it was not -- the very wide confidence interval, again due to compliance issues of getting patients to actually conduct that.

DR. LANGE: Okay, great.

DR. DeFORD: So if you'll notice, you'd see that there were more. We had about 80% follow-up in those patients.

DR. LANGE: Perfect. And the last thing is the smoking and gender and geography issue, I think, is going to become just important to clarify. I notice in your analysis, in Tables 30 and 33, for example, the analysis is done by the entire group, that is, percentage of smokers and non-smokers for the entire group. But only about 85% of them actually had an analysis done, that is, had patency established. So I'm actually interested in what that group -- that is, the percentage of women who actually were evaluated, what percentage of them were smokers and non-smokers -- and men as well -- rather than just in the large cohort, to make sure they're still balanced.

DR. DeFORD: Okay, sure.

DR. LANGE: Thank you.

DR. ZUCKERMAN: Okay, Dr. Lange, that's an excellent set of questions. I just want to clarify one thing in addition. Just to the breakdown of de novo and restenotic percentages, you'd like to see the restenosis rates for those two subgroups, correct?

DR. LANGE: Yes, sir.

DR. ZUCKERMAN: And any other endpoints for those two subgroups.

DR. LANGE: Yes, sir.

DR. DeFORD: Okay.

DR. PAGE: We are past the hour, so only if these are brief clarifying questions. We'll have plenty of time to talk after lunch, I promise. But, again, Dr. Cigarroa and Dr. Posner and Ms. Chauhan, I'll leave it to you as to whether we need to further take questions.

Dr. Cigarroa.

DR. CIGARROA: Do you have data that you could present, following lunch, with regards to the medical therapies that are utilized to treat claudication at follow-up, in terms of those who underwent target lesion revascularization and those who did not in both groups?

DR. DeFORD: Let me make sure I understand. Are you specifically asking for all meds or cilostazol?

DR. CIGARROA: The second.

DR. DeFORD: Okay.

DR. PAGE: And just for the Panel, we're getting to a number of requests that I no longer have these all written down because I can't both chair this and call on people and have these. So I'm going to need your help, before we break, breaking down which of the questions that we are asking the Sponsor to generate in terms of new analyses for the session after lunch and which questions -- we're going to have plenty of time to question the Sponsor about data that they've already shown us, so you're going to need to help me out on that.

Please don't turn on your microphone until you're called on.

Dr. Posner.

DR. POSNER: Very quickly. Since walking distance is such an important thing and these people have comorbidities, when they limit their walking distance, do you make sure it's the claudication and it's not cardiovascular or pulmonary?

DR. DeFORD: Let me make sure I understand. We didn't specifically try to control that or stratify around COPD or other events. Now, we certainly have the information from a demographics perspective for those patients, so I'm not sure I understand what you want us to show.

DR. POSNER: Well, some of the people didn't show improvement in their walking distance and some people did show improvement, and the question is whether the improvement or lack of

improvement was due to cardiopulmonary problems or the claudication. In other words, if you did the test or they self-reported the test and it said, well, you just couldn't walk any further because the claudication was so bad or couldn't walk any further because you were short of breath.

DR. DeFORD: I don't think we've done that analysis specifically that way. I'll see if we can pull that together.

DR. PAGE: Do you have those data? Did you record why they stopped walking or just how far they could walk?

DR. DeFORD: Well, we certainly captured all of the comorbidities, but we didn't capture specifically, did this patient say they can't walk because of COPD or because of claudication?

MS. CHAUHAN: Mine's very brief. On the women between the U.S. and Europe, I would be very interested in the racial configurations.

DR. DeFORD: Okay, we certainly have that information we can provide.

DR. PAGE: Okay, I'm going to try to bring us to break, and we'll reconvene at 10:15. There are a number of questions that were outstanding for further analysis.

Dr. Somberg, can you briefly -- or let me just ask the Sponsor. You had questions about the outcome in patients who received stenting. And, Dr. DeFord, I think, was clear on -- I can't see you, so -- oh, there you are.

DR. DeFORD: I'm sorry, I was putting it down.

DR. PAGE: Were you clear on Dr. Somberg's question?

DR. DeFORD: I believe so. And so we've got a team that's collecting the information, too, so we'll make sure that we come back and provide that information.

DR. PAGE: Great. And, Dr. Zuckerman, you had a question regarding the ratio of 2.0; was that right?

DR. ZUCKERMAN: There were two points. One is similar to Dr. Somberg's, just to get a better feel for how stents compare to this result. And the second one is to better show us that the actual cut-point for the Doppler ultrasound results is not that sensitive to the actual cut-point chosen.

DR. DeFORD: Okay.

DR. PAGE: And, Dr. Cigarroa, you had an issue about the Doppler endpoint?

DR. CIGARROA: I had two questions that I wanted additional data. One was with regards to stratifying the patency endpoint and providing the actual data on the Doppler isolated and then target lesion revascularization. And the second was medical therapy at follow-up by presence or absence of revascularization.

DR. PAGE: Great, thank you.

DR. OHMAN: Dr. Page?

DR. PAGE: Are you clear on that?

DR. DeFORD: Yes, yes. Thank you.

DR. PAGE: And Dr. Simon had --

DR. OHMAN: Dr. Page?

DR. PAGE: -- a question about -- oh, Dr. Ohman, I'll call on you in a second.

DR. OHMAN: Thank you.

DR. PAGE: Dr. Simon had a question about whether there was preserved effect in patients who had -- who did not have target runoff vessels.

DR. SIMON: Right, could they just recalculate the efficacy and safety endpoints with an ITT analysis based on the removal of the zero patency patients in the DCB and the control.

DR. PAGE: Thank you.

And I'm not forgetting about you, Dr. Ohman.

And, Dr. Lange, you said you had four and you gave us five and can you just --

(Laughter.)

DR. PAGE: We got a bonus there. I just want to make sure we're clear on what we're asking the Sponsor.

DR. LANGE: Yeah, I was never good in math. Sorry about that. Do you guys have those five things, or do you need me to go over them

again?

DR. DeFORD: I'm sure that the team in the back has them. I can try to pull back through my notes. So you asked for what drove TLR, restenosis rates by subgroups, de novo and restenotic, geographic miss. You were looking at reference vessel diameter; is that correct?

DR. LANGE: Yes, sir.

DR. DeFORD: And smoking --

DR. LANGE: Do the smoking analysis on the patients who were actually analyzed.

DR. DeFORD: Yes.

DR. LANGE: Thank you. Very good.

DR. PAGE: And, Dr. Ohman, you've been very patient.

DR. OHMAN: Thank you, Dr. Page.

I have a question regarding what variables drove the primary efficacy endpoint. And, in particular, I'm interested in understanding how the geographic region, the sex or gender, and the smoking status actually were predicted in the trial as a whole or the efficacy endpoint, and in this multivariate model, how the treatment assignment related to the studies to say is it a stronger or less strong predictor? It obviously will require some analysis.

DR. DeFORD: And let me make sure I understand that. You were specifically asking about efficacy by geographic region, including sex,

and break that out, and also lesion location. So I want to make sure. Geographic region. You're talking about Europe versus the U.S.?

DR. OHMAN: Correct.

DR. DeFORD: And lesion location, that I've got. Is that correct?

DR. OHMAN: Yes, it's to understand if these subgroups that we have found interaction, how important they are in the overall trial of predicting what the outcome of the trial, i.e., the efficacy endpoint, would be. So are they important, moderately important, or not that important?

DR. DeFORD: Okay. And I think we could easily provide you -- we had a number of prespecified covariates, and we did analyses on all of those. We could probably pick these out and summarize them, if that is meeting your expectation.

DR. OHMAN: That would be fine.

DR. DeFORD: Thank you.

DR. PAGE: With that, I'm going to have us take a break. We're going to shorten the break but still give 10 minutes. So we'll go until 10:20 in case people have to check out. So instead of reconvening at 10:15, we'll make it 10:20.

Panel members, please do not discuss the meeting topic during the break among yourselves or with any member of the audience. And, again, we'll resume at 10:20.

Thank you.

(Off the record.)

(On the record.)

DR. PAGE: I'd like to call us back to order. And it's now time for the FDA to give their presentation. I would point out that the Sponsor has set a high bar by being ready on time and keeping it under 90 minutes, and we're expecting the same from the FDA.

Thank you.

MS. PACK: Hello, my name is Lindsay Pack, and I am the lead reviewer for the PMA under discussion today. Today we will be talking about the Bard Lutonix 035 Drug-Coated Balloon PTA Catheter, which is a first-of-a-kind device.

For FDA's portion of the presentation, I will start out by providing the introduction and background information. Dr. Donna Buckley will then describe the key characteristics of the clinical study design and results. Following Dr. Buckley's presentation, Dr. Terri Johnson will provide the statistical perspective of the pivotal study, including FDA's analyses. And then Dr. Dale Tavris will describe the Sponsor's proposed post-approval study as well as the limitations that FDA has identified with the study design. At the end, I will summarize the key areas for which we would like Panel input.

Before we get into the details of the clinical study, I would like to provide you some relevant background information. This will be the agenda for the first portion of the presentation.

I would like to point out that this device is considered a combination product that consists of both drug and medical device. The PTA balloon provides the mechanical action of dilating the stenosis, thereby opening the vessel, which is considered the primary mode of action. For this reason, the combination product is reviewed under the purview of the Center for Devices and Radiological Health with input and consulting reviews from the Center for Drug Evaluation and Research. All of the groups listed on this slide participated in the review of this device.

Specifically, I would like to acknowledge the reviewers listed on this slide that directly participated in the review of the data provided as part of the PMA and/or the original IDE.

Today we are here to discuss the Lutonix 035 Drug-Coated Balloon PTA Catheter, which is a first-of-a-kind device and the reason we are requesting Panel input.

As I mentioned previously, this device is a combination product which consists of a PTA catheter and a drug coating which is located on the surface of the balloon portion of the catheter. The drug coating is a non-polymer based formulation consisting of 2 $\mu g/mm^2$ of the active ingredient, paclitaxel, as well as excipients comprised of polysorbate, sorbitol, and methanol. The Sponsor is requesting approval of the device in sizes 4 mm to 6 mm in diameter and 40 mm to 100 mm in length. Each size will have the same drug coating, drug dose per unit area, and thus the total

amount of drug increases both with length and balloon diameter.

The Sponsor has proposed the device to be indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions ≤ 15 cm in length in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.

FDA would like to point out that all of the clinical data that has been provided to date has included pre-dilatation of the target lesion from a non-coated balloon to approximately 1 mm less than the reference vessel diameter prior to use of the subject device.

In the Sponsor's currently proposed labeling, provided for you in Tab 7 of your Panel Pack, the Sponsor does not discuss the need for pre-dilatation in either the proposed indication or the instructions for proper use of the device. It is FDA's general goal that the indication for use reflects that of the clinical study and that the instructions provide sufficient details to inform the user. As you will note in your list of questions for Panel discussion document, this is an area for which FDA would like the Panel's input.

I would now like to take a quick moment to briefly go over some of the key regulatory milestones leading up to today's meeting.

After approval of their Investigational Device Exemption, Lutonix began enrolling in the Lutonix drug-coated balloon study, known as the LEVANT 2, in July 2011. A year later they completed enrollment in their randomized pivotal study, which includes patients in the U.S., Germany,

Belgium, and Austria.

Although paclitaxel has been studied in some already approved devices, the use of paclitaxel here is quite different; specifically, compared to other approved technology, there is a high drug dosage. Additionally, the coating is designed to come off rapidly in the body instead of being contained in a polymer coating that is intended to slowly elute over time. Because of these differences, there are increased risks related to toxicity as well as particulates.

Given the nature of this first-of-a-kind device, the relatively high drug dosage, and the high level of particulates generated, FDA believes that in order to evaluate the safety of this device, there should be sufficient power to detect events that may occur 1% to 2% of the time.

However, in order to be least burdensome, FDA did not require that all of this data be generated as part of the randomized pivotal study. Instead, FDA requested that the Sponsor propose a method for collecting this additional safety data. Lutonix chose to collect this via a continued access registry, which began at the IDE investigational sites upon completion of enrollment of the pivotal study. In order to add additional sites, an identical protocol was approved. Together, these two pieces make up the LEVANT 2 safety registry.

The final module of the PMA was filed on November 25th, 2013. The Sponsor included in their analysis the full LEVANT 2 pivotal study

cohort in their submission of the PMA. However, because the majority of the patients have not yet reached one year of follow-up, the Sponsor did not include all of the LEVANT 2 safety registry data that was requested. Although this would have been grounds for not filing the PMA, the amount of available follow-up data was not apparent until after the first round of deficiencies.

I'm not going to go into the details of the review of the preclinical data at this time. However, I would briefly like to mention that the Sponsor submitted a variety of test data intended to support the safety and effectiveness of this device.

Now that we've gone through a little bit of the background information, we will transition to a discussion of FDA's review of the clinical study, followed by a summary of the Sponsor's proposed post-approval study should this device be approved. During these presentations, each of the reviewers will highlight the key areas for which we would like Panel input. If you follow along with the questions for Panel document, you will see these same topics listed. I have already discussed the indications for use and labeling, which are Questions 7 and 8 of the document, but the remainder will be discussed in the presentations to follow.

I would now like to ask Dr. Donna Buckley to come to the podium.

DR. BUCKLEY: Good morning. I'm Donna Buckley. I am an interventional radiologist in the Division of Cardiovascular Devices in the

Office of Device Evaluation.

Today I plan to summarize the clinical experience with the Lutonix drug-coated balloon used to treat SFA lesions, with particular focus on the pivotal LEVANT 2 randomized controlled trial and the LEVANT 2 safety registry. I'll then offer some concluding statements.

There are several trials that have been completed or are under way and are designed to evaluate the Lutonix drug-coated balloon.

The LEVANT 1 randomized study was a European study that included 101 patients and a slightly different device design and served to evaluate initial safety and performance. Although there are significant similarities in the devices used in the LEVANT 1 and the LEVANT 2 trials, the LEVANT 1 results are not directly applicable to the device planned for marketing, since it included a one-eight system and used hand-folding the balloon.

The LEVANT 2 pivotal trial was a 2:1 randomized trial including sites in the U.S. and outside the U.S., including 543 patients, and this served to evaluate pivotal safety and effectiveness and is the primary dataset in this PMA application.

The LEVANT 2 safety registry includes continued enrollment of patients after LEVANT 2 trial enrollment was completed. These groups are labeled as either "continued access" if patients were treated at LEVANT 2 study sites, or "additional safety" if patients were enrolled at non-LEVANT 2

sites. Regardless, the same protocol was used, and data from these patients are combined and referred to as the safety registry.

The purpose of the safety registry was to generate additional data to assess for rare adverse events in the 1% to 2% range, primarily to support full evaluation of the potential impact of the drug component. However, incomplete follow-up information is available to test the hypothesis that's planned.

Finally, the Sponsor has initiated a 1,000-patient global SFA registry to capture data on real-world device use in a heterogeneous clinical practice population.

I'd like to focus comments this morning on the LEVANT 2 pivotal randomized study and the LEVANT 2 safety registry.

Starting with the LEVANT 2 trial, it included enrollment of 543 patients which were randomized in a 2:1 fashion to either drug-coated balloon or PTA alone. Of the 476 randomized patients, there were 429 patients who had 12-month analyzable data for the primary intent-to-treat, or ITT, analysis for safety and 399 patients with analyzable data for effectiveness.

As the Sponsor previously noted, the difference between the safety and effectiveness follow-up denominators is related to the fact that safety assessment only required clinical follow-up, whereas effectiveness assessment required additional imaging follow-up. Overall follow-up

compliance in the various cohorts ranged from 85% to 90%. In general, follow-up compliance in the study is similar to other femoropopliteal PMA trials and considered adequate.

In addition to the randomized cohort, there were 56 roll-in patients and 11 patients treated per standard practice, where the standard practice patients were those who had a flow-limiting dissection or residual stenosis > 70% during the pre-dilatation phase. These patients were not randomized and treated per operator and institutional practice.

After randomization, there were patients who required bailout stenting following treatment with the randomized device. This included 8 drug-coated balloon patients and 11 PTA-alone patients, and these were patients who had greater than 50% stenosis and a pressure gradient. Also these patients were not considered immediate primary endpoint failures. So it was favorable, regarding trial conduct, that there were a limited number of patients treated per standard practice and who required bailout stenting after randomization.

The LEVANT 2 trial included patients with Rutherford 2 to 4, that is, patients with claudication to rest pain without tissue loss. The lesions were to be > 70% stenotic, < 15 cm in length, and between 4 mm to 6 mm in diameter. There was the allowance to treat inflow disease during the index procedure. However, treatment of outflow disease and use of any adjunctive treatment modalities such as atherectomy was prohibited.

In general, baseline characteristics regarding demographics, selected medical history, clinical characteristics, concomitant medication use, and lesion characteristics were similar between groups.

There were statistically significant differences in some procedural characteristics, however. In particular, compared to the control arm, the drug-coated balloon arm had lower inflation pressures, shorter inflation times, fewer grade C dissections, less bailout stenting, and less geographic miss, where geographic miss occurred when the entire pre-dilated injury segment was not treated with the randomized device, as assessed by the angiographic core lab.

One may propose that these differences in procedural characteristics are likely related to a procedural basis, since the procedure physician could not be blinded to treatment group.

Looking at the primary endpoints, the primary safety endpoint included a composite of freedom from 30-day death and a freedom from one-year index limb amputation, re-intervention, and index limb-related death.

The statistical hypothesis is noted here and was proposed to demonstrate that safety events in the drug-coated balloon group could be no more than 5% in excess of those in the PTA group, with a one-sided alpha of 0.025.

For this primary safety endpoint, the ITT analysis showed that the drug-coated balloon was non-inferior to PTA alone using a 5% margin.

The observed rate in the drug-coated balloon arm was 83.9% and the PTA group was 79.0%. The p-value was significant at 0.005.

Looking at the individual components of the composite safety endpoint, we see that there were no periprocedural deaths, no index limb-related deaths at 12 months, and only one amputation in the drug-coated balloon arm. Target limb revascularization at 12 months occurred at a rate of 15.4% in the drug-coated balloon group and 21% in the control group. So we see that target limb revascularization is serving as the primary driver for the safety assessment.

If we were to look at the prespecified per-protocol analysis, which excluded patients when the assigned treatment was not given, there was no pre-dilatation. Site-reported lesion lengths were greater than 15 cm. There was treatment of outflow disease, thrombectomy was performed, or there was core lab reported geographic miss. We see that with the exception of four patients who had outflow disease treated and one patient who had intra-procedural thrombectomy, the vast majority of excluded patients (59) were on the basis of geographic miss.

Non-inferiority of the drug-coated balloon was not demonstrated in the per-protocol analysis, with a non-significant p-value of 0.08. So, here, the overall conclusion from the prespecified per-protocol analysis is discordant with the ITT results.

For the intent-to-treat analysis, the average estimate for the

difference in safety between the arms was 4.9%, in favor of the device arm, with a range from -2.6 to 12.3.

For the per-protocol analysis, the average estimate was 0.7%, also slightly in favor of the drug-coated balloon arm, with a range from -7.3 to 8.7.

Looking at effectiveness, the primary effectiveness endpoint included the composite of freedom from binary restenosis, as adjudicated by the core lab, and freedom from target lesion revascularization, as adjudicated by the clinical events committee.

The statistical hypothesis is noted here and was proposed to demonstrate that the primary patency in the drug-coated balloon group was superior to that of the PTA group, with a two-sided alpha of 0.05.

For the primary effectiveness endpoint, the ITT analysis showed that the drug-coated balloon was superior to PTA alone. The observed rate in the drug-coated balloon group was 65.2% and in the PTA group was 52.6%. The p-value was significant at 0.015.

Looking at the individual components of the composite effectiveness endpoint, we see that TLR, or target lesion revascularization, accounted for approximately 38% of events in both groups. Correspondingly, adjudicated restenosis accounted for approximately 62% of events in both groups. So reasons for failure of primary patency were similar for drug-coated balloon and PTA alone, and the primary effectiveness endpoint was

primarily driven by the restenosis rate.

Looking at the prespecified per-protocol analysis for effectiveness, the difference in patency between the two groups is reduced compared to the ITT analysis, and a conclusion of superiority was not demonstrated with a non-significant p-value of 0.11.

For the intent-to-treat analysis, the average estimate for effectiveness was 12.6%, in favor of the device arm, with a range from 2.4 to 22.8.

For the per-protocol analysis, the average estimate for effectiveness was 9.3%, also in favor of the drug-coated balloon arm, with a range from -2.1 to 20.7. Nonetheless, the per-protocol results were not significant and did not replicate the ITT analysis results.

Again, the primary basis for this finding was related to geographic miss, where geographic miss was a predefined criterion for the per-protocol exclusion, developed with the intent to target cases where drug was not applied across the entire pre-dilated segment.

Actually, the study results demonstrated a larger proportion of patients excluded from the control arm, instead of the drug-coated balloon arm, on the basis of geographic miss. And upon reflection, this finding is clinically plausible and may reflect the unblinded operator's careful usage of the new drug-coated balloon and reversion to more of a standard of care treatment in the control arm, where operators are less rigorous about

matching previously inflated segments and are more focused on complete treatment of a lesion until an acceptable angiographic result is obtained.

There were a number of planned secondary endpoints that were to be tested in a hierarchical fashion. If the first hypothesis fails to demonstrate significance, the remainder were not tested.

The first endpoint planned to be tested typically carries the highest clinical importance and corresponds to desired labeling claims. In this study, the Sponsor prespecified the total TLR at 12 months as their first secondary endpoint to be hypothesis tested. However, the Sponsor was unable to demonstrate significant improvement in 12-month TLR with a non-significant p-value of 0.208. Therefore, the other endpoints were not hypothesis tested.

The descriptive outcomes of the other two 12-month endpoints are also listed here and include total TVR at 12 months and composite safety at one month -- excuse me -- composite safety at 12 months.

When assessing the robustness of the primary effectiveness endpoint to different Doppler ultrasound definitions, we see that there is significant benefit of the drug-coated balloon when all core lab adjudications are accounted for, which includes consideration of PSVR as well as other factors. This served as the primary analysis in the current study.

In addition, the drug-coated balloon performs better than PTA alone, with a PSVR cutoff of 3.0 as well as that of 2.5. However, at a cutoff of

2.0, significance is no longer demonstrated.

Looking at the available longer-term data, particularly for 24-month primary patency, in this Kaplan-Meier analysis we see that the difference in patency at 12 months, favoring the drug-coated balloon, is less pronounced at 24 months. We also note that the flattening of the curves between 12 and 24 months are partially reflecting patients awaiting follow-up.

Finally, it's also important to note that follow-up is incomplete with 26 drug-coated balloon subjects and 14 PTA subjects at risk at the 24-month time point.

Although these findings are preliminary, our conclusions are limited, and longer-term data are needed to clearly define the durability of the drug effect.

Turning our attention to sub-analysis, with particular attention to gender and geography findings, first, looking at gender, we see a significant interaction for primary patency, where significance is evaluated at the 0.15 level. Here, there is a higher treatment effect of the drug-coated balloon for males versus females, with a p-value of 0.01.

In fact, a comparison of the observed rates suggests a trend towards better primary patency in females with PTA alone. Here, the observed primary patency rate in the PTA arm was 61.4%, which was better than that of the drug-coated balloon arm, which was 56.4%, yielding a

difference of 4.9% in favor of the PTA arm. This is in contrast to the male group that demonstrated a 22.2% difference in favor of the drug-coated balloon arm.

Here, performance in the female population is not an issue that women may not have a similar degree of benefit with the drug-coated balloon compared to the male population, but that overall women actually had a trend for better outcomes with the control device. So, in general, the male results are primarily driving the overall study conclusions regarding effectiveness.

Turning our attention to geography, we see that the treatment effect of the drug-coated balloon regarding safety is higher for OUS patients, with a p-value of 0.02 for the interaction.

Similarly, we see that the treatment effect of the drug-coated balloon regarding effectiveness is higher for OUS patients, with a p-value of 0.12 for the interaction. Note that the significance was tested at a 0.15 level.

Statistically significant interaction of treatment effect with geography was noted, where OUS patients performed better with the drug-coated balloon, compared to the U.S. patients, for both primary safety and effectiveness. Furthermore, the OUS results are primarily driving the overall study conclusions, such that poolability is not clearly supported.

The Sponsor performed an exploratory analysis and concluded that smoking status had a significant impact on the results of the primary

effectiveness endpoint and is a better statistical predictor of outcome compared to gender or geography. Nonetheless, one is left with uncertainty regarding the clinical significance of this post hoc analysis. There is the suggestion that the variation in treatment effect by geography and gender is driven by an outlier result for the non-smoking U.S. female population, since this particular subset had comparably unfavorable baseline characteristics. Nonetheless, overall randomization successfully balanced baseline characteristics for the overall ITT population.

The subgroup interactions were unexpected. Following FDA review, information was not obtained to support an expected gender treatment effect, nor could we clearly explain why results outside the United States would be expected to be different. Hence, questions remain regarding the subgroup analysis results regarding gender and geography. Dr. Johnson will provide a more detailed discussion regarding these issues.

Turning our attention to the LEVANT 2 safety registry, the registry was designed to detect rare adverse events in a 1% to 2% range, primarily to support full evaluation of the potential impact of the drug component.

In order to test the hypothesis at 12 months with 869 evaluable patients, there was planned enrollment of a total of 1,022 drug-coated balloon patients to account for 15% lost to follow-up. This was to include a combination of the roll-in, randomized, and safety registry patients. To date,

1,029 patients have been enrolled, and there is 12-month data available on 561 of these patients.

At the time of PMA submission, FDA expected and the Sponsor agreed to provide 12-month data on at least 50% of patients. This approach was taken based on enrollment rates and FDA's expectation that we may have updated data on nearly 100% of patients followed to 12 months, prior to Advisory Panel review, in a least burdensome approach. And this is consistent with the recommendations FDA has given to all companies studying similar technologies.

Unfortunately, even with the latest clinical update during PMA review, we have approximately 60% of 12-month data available for review. This does not meet the required sample size per the original hypothesis-testing plan.

From the combined data available to date, however, there have been no unanticipated adverse events or drug-related events, and currently the composite freedom from safety events at 12 months is in excess of 90%, which exceeds the point estimate in the LEVANT 2 randomized study arm.

In conclusion, the LEVANT 2 study was generally well conducted with respect to controlling bailout stenting and having adequate follow-up compliance.

In addition, independent third-party review, follow-up assessments performed by physicians blinded to treatment, and patient

blinding helped to reduce bias. However, a component to procedural bias appears to have been introduced.

The LEVANT 2 primary ITT analysis results demonstrated superior effectiveness and non-inferior safety with a margin of 5%. However, these findings were not replicated in the prespecified per-protocol analysis, primarily on the basis of geographic miss.

There are questions that remain regarding the subgroup analyses where effectiveness of the drug-coated balloon was established in males, which is driving the results. However, benefit of the drug-coated balloon was not clearly demonstrated in females.

Separate assessment of the LEVANT 2 results in the United States and outside the United States shows that, overall, there was better performance with the drug-coated balloon outside the United States, which is driving the overall study conclusions.

The prespecified hypothesis testing of the secondary endpoint of 12-month target lesion revascularization did not show superiority of the drug-coated balloon compared to PTA alone.

Also the duration of the clinical impact of the drug coating has also not been fully established, such that the long-term benefit regarding primary patency is unclear at this time.

Finally, there have not been any reported unanticipated or drug-related adverse events in the safety registry, although current follow-up

is incomplete to assess for events as planned for the original protocol.

Thank you. And I'd like to introduce Dr. Terri Johnson, who will give FDA's statistical summary.

DR. JOHNSON: Good morning. I'm Dr. Terri Johnson, and I will present the FDA's statistical review of the LEVANT 2 pivotal trial. Please note that LEVANT 1, continued access, and registry data are not presented here.

I will briefly discuss some features of LEVANT 2, such as blinding of the treatment assignment and analysis population. I will then present results of the primary endpoints. In particular, I will focus on the impact of the discussed features of the study design on these results. Also I will discuss pooling of the outside of U.S. data and the U.S. data. In addition, I will present results of gender analysis and the prespecified secondary endpoints from a statistical perspective. Then I will end with statistical conclusions.

The LEVANT 2 pivotal trial is a prospective, multicenter, single-blinded, 2:1 (test:control) randomized trial comparing test Lutonix DCB to control PTA.

Please note that data presented here today are not the data submitted to the PMA originally. The statistical analysis plan was approved by the FDA on September 12th, 2013. The PMA was filed on November 25th, 2013. In the PMA, a protocol with a new statistical analysis plan was included after unblinding of the data and submitted results based on this unapproved

protocol.

Upon FDA's request during the PMA review process, updated data were received on March 20th, 2014, and the Sponsor reanalyzed the updated data according to the FDA-approved protocol and the statistical analysis plan. And these are the data and analyses presented today.

All subjects, duplex ultrasound operators, core lab evaluators, follow-up investigators, clinical events committee were blinded to treatment assignment. However, those investigators who administered the treatments were not blinded to the treatment assignment.

The intent-to-treat population was defined as all these subjects who were enrolled and randomized to a treatment group, and the intent-to-treat population was analyzed according to the randomization assignment regardless of the actual treatment received.

The per-protocol population excluded subjects with predefined major protocol violations and were then analyzed according to their randomization assignments.

All subjects received the assigned treatments from randomization, so the intent-to-treat population and the as-treated population were the same. The intent-to-treat population was prespecified as the primary analysis population.

There were a total of 476 subjects enrolled and randomized, and therefore these subjects make up the intent-to-treat analysis population.

Among these, 92% in the test Lutonix DCB group but only 76% in the control PTA group consisted of the per-protocol analysis population.

Please note the imbalance in the exclusion from the per-protocol analysis population between the two treatment groups, mainly due to geographic miss. This imbalance suggests that there may be a procedural bias introduced by unblinded investigators. And if there is an apparent procedural bias introduced by unblinded investigators, including these patients in the intent-to-treat analysis may bias the treatment effect. Then the per-protocol analysis may be more appropriate for this study. Therefore, it is important to note not only the imbalance of geographic miss between the treatment groups, but also how this imbalance may have influenced the outcome results.

In particular, there was a bigger imbalance in geographic miss between the two treatment groups outside the U.S. The variation in geography will be discussed in more detail later. For now, please keep in mind that the potential procedural bias implied by the imbalance of geographic misses between the treatment groups may produce biased treatment effects.

The primary safety endpoint was tested for non-inferiority at a one-sided significance level of 0.025 with a non-inferiority margin of 5%, which means that the lower bound of the 95% confidence interval of the difference in the primary endpoint rates must be greater than -5% to meet

the objective.

The results of the primary safety endpoint were presented earlier by the Sponsor and Dr. Buckley. Please note that these results were based on the available complete case data. Also keep in mind that these analyses assume that the outside the U.S. and the U.S. data can be pooled.

Under the intent-to-treat analysis population, the lower bound of the 95% confidence interval of the rate difference was greater than -5%. However, under the per-protocol analysis population, the lower bound of the 95% confidence interval was less than -5%. So the ITT and the per-protocol analyses yield different conclusions on the non-inferiority of the test device compared to the control PTA.

The rates of the primary safety endpoint were different between the two treatment groups among those who were excluded from the per-protocol analysis. There were more successes in the test Lutonix DCB group than the control PTA group. Hence, including these patients in the ITT analysis would make the result become more favorable for the test device, as forewarned previously. And this bias did increase the treatment effect in the ITT analysis to become significant.

In the previous slides we have discussed overall results for the primary safety endpoint. The overall results assume that the data from all sites and regions can be pooled.

Now, here are the results for the primary safety endpoint

separately for the outside of U.S. and the U.S.

There was a significant interaction between geography and treatment group. The p-value for the interaction was 0.02. Therefore, the OUS and the U.S. data should not be pooled for the evaluation of the primary safety endpoint. The data show that overall combined results were driven by the OUS data, and the data did not show that the test Lutonix DCB was non-inferior to the control PTA within the U.S. Although not statistically significant, the control PTA showed safer outcome than the test Lutonix DCB in the U.S.

Results for the primary safety endpoint under the intent-to-treat analysis may be biased due to possible procedural bias. The overall treatment effect may be overestimated in the ITT analysis, and therefore, the per-protocol analysis may be more appropriate. The OUS and the U.S. data cannot be pooled for the evaluation of the primary safety endpoint from a statistical perspective, and the test Lutonix DCB did not establish the non-inferiority over the control PTA within the U.S.

The primary effectiveness endpoint is tested for superiority of the test Lutonix DCB over the control PTA at a two-sided significance level of 0.05. Therefore, the lower 95% confidence interval of the difference in primary patency rate at one year must be greater than 0 to meet the objective.

Under the intent-to-treat population with complete case data,

the 95% confidence interval of the rate difference excluded zero. However, there was no statistical difference in the primary patency rate at one year between the treatment groups for the per-protocol population.

Again, conclusions from the ITT analysis and the per-protocol analysis were different, and the bias introduced seems to have overestimated the treatment effect in the intent-to-treat analysis. Hence, similar to the evaluation of the primary safety endpoint, the per-protocol analysis may be appropriate in the evaluation of the primary effectiveness endpoint.

Furthermore, the analysis suggests that the OUS and the U.S. data may not be pooled for the evaluation of the primary effectiveness endpoint. The significant difference in the overall primary patency rate at one year was driven by the OUS data and the similar effectiveness of the test Lutonix DCB was not shown within the U.S.

Results for the primary effectiveness endpoint under the intent-to-treat analysis may be biased due to possible procedural bias. The overall treatment effect may be overestimated in the ITT analysis, and therefore the per-protocol analysis may be more appropriate. It is not clear that the OUS and the U.S. data can be pooled for the evaluation of the primary effectiveness endpoint from a statistical perspective. And the test Lutonix DCB was not more effective compared to control PTA within the U.S.

Following the FDA Draft Guidance on Evaluation for Sex Differences in Medical Device Clinical Studies, a subgroup analysis on gender

was performed. The gender and treatment group interaction test was prespecified in the protocol. There was a significant qualitative interaction between gender and treatment group for the primary effectiveness endpoint, with a p-value of 0.01. In other words, the treatment effects for female and male were in opposite direction, with a primary patency rate at one year for the control PTA group being greater than the test Lutonix DCB group for the female.

To further explore the gender variation, covariates were examined. These covariates were prespecified in the protocol to have potential impact on study results. Along these prespecified covariates, only Rutherford grade showed significant imbalance in distribution among gender and treatment group. And after adjusting for covariate with a significant imbalance, the difference in the primary patency rate at one year was still in favor of the control PTA group over the test Lutonix DCB group in female.

FDA also observed that there was a significant three-way interaction between geography, gender, and treatment group. Stratified analysis on geography and gender showed that OUS females showed favorable results of the control PTA group for the primary effectiveness endpoint. Therefore, the FDA further examined the prespecified covariates to assess whether there is any imbalance between the two treatment groups within the U.S. females. In general, there were no imbalances except perhaps for ankle-brachial index of target limb.

The Sponsor has suggested that it was smoking status that had significant impact on the results of the primary effectiveness endpoint within the U.S. females. However, proportion of smokers in two treatment groups were comparable within the U.S. females.

Nevertheless, the FDA utilized propensity score method to adjust for any potential imbalance in these covariates. Propensity score here is a conditional probability of receiving the test Lutonix DCB device over the control PTA, given these prespecified covariates. Advantage of propensity score method is that it reduces bias and it does not involve outcome data when calculating the propensity scores. I will not get into technical details of how the propensity score was calculated. However, please keep in mind that the study was not sufficiently powered to perform such subgroup analyses.

After adjusting for the propensity score, the difference in rates of the primary patency rate at one year was -13.2%, still in favor of the control PTA over the test Lutonix DCB.

There were nine secondary endpoints prespecified in the protocol for hypothesis testing. A hierarchical method was implemented to control for overall Type I error rate. Under the hierarchical method, each endpoint is tested at a significance level of 0.05, but the lower ordered endpoint will not be tested unless the hypotheses for the higher ordered terms all had p-values of 0.05.

Please note that these nine secondary endpoints were ordered

based on clinical meaningfulness, but also based on the Sponsor's priority to make claims in the label.

The p-value for the first ordered secondary endpoint, total target lesion revascularization at 12 months, was 0.21. According to the prespecified hierarchical order, since the first secondary endpoint failed its hypothesis test, all secondary endpoints failed the hypothesis tests.

Here are the FDA's statistical conclusions.

1. Conclusions from the ITT and the per-protocol analyses were different. There were imbalances of major protocol deviation between the treatment groups. A greater proportion of the control PTA group had geographic miss, which suggests that there were procedural biases introduced by unblinded investigators, and this may have biased the results of the overall ITT analysis.

Please provide comments on the implication of the imbalance in geographic miss between the two treatment groups, specifically why the OUS may have bigger imbalances of geographic miss and the impact of these imbalances on the treatment effects.

2. Pooling the OUS and the U.S. data to evaluate the performance of the test device compared to the control PTA is a major concern. The results of the primary safety and the primary effectiveness endpoints outside the U.S. were different than those in the U.S. The favorable results observed overall were driven by the OUS data and similar

results were not observed in the U.S. data. The study may not meet the primary ITT safety and effectiveness endpoints within the U.S.

3. There was no statistical evidence that the study device is effective for U.S. females. The primary patency rate at one year was higher in the control PTA group than the test Lutonix DCB group for the U.S. females.

4. All secondary endpoints failed their objectives. Therefore, whether there is any added benefit from the test device is questionable from a statistical perspective.

This concludes the FDA's statistical review of the LEVANT 2 pivotal trial of the Lutonix DCB.

Next, Dr. Tavris will present the review of the proposed post-approval study.

DR. TAVRIS: Good morning. My name is Dale Tavris, and I am a physician/epidemiologist from the Division of Epidemiology in the Office of Surveillance and Biometrics.

Before I talk about the post-approval study, we will clarify a few things.

The discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean that FDA is suggesting that the device is safe and effective.

The plan to conduct a post-approval study does not decrease the threshold of evidence required by FDA for device approval.

The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and appropriate risk/benefit balance.

Through review of the premarket data, the FDA review team has identified postmarket concerns that should be addressed if this first-of-a-kind device is approved. These include, first, long-term (that is, two to five years) performance of the device, given that premarket data has only been provided up to one year for the majority of the pivotal study patients, and the limited two-year data provided raise questions about the longer-term durability of the drug effect; and, secondly, performance of the device in women, since premarket data regarding device performance in women raises significant concerns, as you've already heard.

For analytical and descriptive analysis, the Sponsor proposes extended follow-up of the subjects from the LEVANT 2 pivotal trial, including 316 subjects randomized to use of the device, 160 PTA controls, and 56 roll-in device users, and also 657 subjects from the LEVANT 2 safety registries. In addition, for descriptive ancillary analysis only, the Sponsor proposes to utilize up to 1,000 subjects from the global SFA registry. These subjects are not included in the proposed hypothesis testing, and the Sponsor has thus far proposed no details on how this data will be analyzed.

The design of the proposed post-approval study is a multi-site, two-armed observational prospective cohort study with five-year follow-up.

The proposed sample size for the testing of the study hypotheses is 1189. This includes the previously noted 532 subjects from the LEVANT 2 pivotal IDE study, including 372 device users and 160 PTA controls, plus an additional 657 subjects from the LEVANT 2 safety registry studies.

The five-year follow-up includes duplex ultrasound and clinical follow-up through two years, followed by telephone follow-up only annually for years three through five.

The Sponsor proposes three main endpoints, two of which are accompanied by hypothesis testing. The effectiveness endpoint is primary patency at two years, defined as absence of target lesion restenosis and target lesion revascularization. The hypothesis is that primary patency at two years in the subject group is superior to that of the PTA control subjects from the pivotal trial.

The main safety endpoint is composite freedom from all-cause perioperative death and index limb amputation at 12 months and index limb re-intervention at 12 months and index limb-related death at 12 months. The hypothesis is that freedom from the composite events will be non-inferior with a 10% margin to that of the PTA control subjects from the pivotal trial.

The other primary safety endpoint is the rate of unanticipated device- or drug-related adverse events through five years. The Sponsor proposes no hypothesis testing with respect to that endpoint.

FDA is concerned about the Sponsor's proposal to limit

assessment of the main safety endpoint to one year and assessment of the main effectiveness endpoint to two years. Related to that concern is the Sponsor's plan to limit follow-up after two years to telephone assessment only.

The testing of the hypotheses by comparing device subjects with controls is somewhat problematic because of the potential lack of comparability between controls and subjects. Only a portion of subjects in the post-approval study -- those from the pivotal trial -- will be compared with a concurrent control group.

Key issues for Panel consideration include the following:

First, the substantial gender differences in the data from the pivotal trial are surprising and perplexing. Overall, the primary effectiveness results in women are inferior to those in men and are a point of concern to the FDA. To address this issue, an assessment of important endpoints by gender should be performed as part of the post-approval study.

An important issue to FDA is whether assessment of female patients already enrolled in the post-approval study would adequately address this concern or if new enrollment is needed. In this regard, please note that only 35% of the one-year safety registry data has been provided to the FDA to date, leaving 65% yet to be evaluated.

Specification of an adequate sample size would require the identification of what would constitute acceptable results and a best estimate

of what results we would expect.

Secondly, the Sponsor's proposed post-approval plan to assess the main safety endpoint at one year and the main effectiveness endpoint at two years is of concern to FDA, and it is inconsistent with previous post-approval studies that have been approved for evaluation of similar disease. Those studies included primary assessment at three years and additional follow-up of patients at five years, primarily to evaluate drug-related safety issues.

The main reason that the Sponsor has limited their effectiveness evaluation to two years is that their patients were consented to only two years of office visits and five years of telephone follow-up. Therefore, in the absence of re-consenting enrolled patients, new enrollment would be needed to obtain longer-term follow-up data.

And, thirdly, as I noted in the discussion from my previous slide, for the purpose of hypothesis testing, there are potential problems with regard to the comparability of the proposed control group with the Lutonix device users. Options for comparator groups may include a concurrent control group, a historic control group, or generation of performance goals.

That concludes my presentation. And now Lindsay Pack will present FDA's concluding remarks.

MS. PACK: Thank you, Dr. Buckley, Dr. Johnson, and Dr. Tavris, for the nice presentation of FDA's review.

In conclusion, although some of the elements of the nonclinical testing are still under review, FDA has no safety- or performance-related concerns from the in vitro data.

The LEVANT 2 primary intent-to-treat analysis suggested that the drug-coated balloon had superior effectiveness with regard to 12-month primary patency and non-inferiority safety with a margin of 5%. The prespecified per-protocol analyses for safety and effectiveness, however, did not replicate the intent-to-treat findings. From a statistical perspective, the per-protocol adds value because it helps reduce bias regarding geographic miss. However, the clinical relevance of this finding is uncertain.

There are significant questions that remain regarding the subgroup analyses, where effectiveness of the drug-coated balloon was established in males, which is driving the results. However, the benefit of the drug-coated balloon was not demonstrated in females.

Separate assessment of the LEVANT 2 results in the United States and outside of the United States shows that there was better performance of the drug-coated balloon outside of the United States, which is also driving study conclusions. And based on these results, from a clinical perspective, the poolability of the U.S. and OUS data is questionable. However, the clinical reason behind this observation is unclear.

Pre-specified hypothesis testing of the secondary endpoint of 12-month target lesion revascularization did not show superiority of the drug-

coated balloon compared to PTA alone, although the point estimates favor drug-coated balloons.

The duration of impact of the drug coating has not been fully established, such that long-term benefit regarding primary patency is unknown.

Finally, FDA has significant concerns that the Sponsor did not provide the agreed-upon amount of follow-up data from the safety registry that is needed to evaluate the potential issues related to rare drug effects that could be caused by this very different usage of paclitaxel than has ever been previously evaluated.

Of the 1,029 drug-coated balloon patients enrolled from the combined pivotal and continued access studies, 12-month safety data has only been provided on 561 of them, leaving approximately 45% of the patients not presently considered. And this is inconsistent with the recommendations that FDA has communicated to all companies for the amount of data that should be provided at the time of PMA.

As I mentioned during the introduction, these are the key discussion points for which we would like Panel input, as noted in the questions per Panel document. Specifically, as discussed here today regarding safety, we would like you to discuss the differences in the intent-to-treat and per-protocol analyses and the lack of agreed-upon follow-up in the safety analysis to detect rare adverse drug effects.

For effectiveness, we would also like you to comment on the differences in the intent-to-treat and per-protocol analyses, as well as the lack of statistical difference in the target lesion revascularization rates between drug-coated balloon and PTA arms.

As there were some interesting interactions identified in the gender and geography subgroup analyses, we would like you to comment on the clinical significance of these issues and any impact this may have on the post-approval study analyses.

Furthermore, we would like you to comment on the data available for long-term follow-up.

Finally, after discussing these key issues, we will ask you to consolidate those thoughts into a discussion of the overall benefit/risk of the device, followed by any recommendations regarding the post-approval study, indications, or labeling.

Thank you all for participation in today's important meeting. We look forward to hearing your thoughts.

DR. PAGE: I want to thank the FDA for an excellent presentation. And you kept it on time beautifully, as well. And we appreciate that, as well.

I'll now ask the Panel if they have any brief clarifying questions for the FDA. And please remember that the Panel may also question the FDA during the Panel deliberation session later this afternoon.

Dr. Somberg.

DR. SOMBERG: Well, that was a very nice presentation. And, in fact, both presentations were excellent for the Sponsor and the FDA.

The gender issue is very concerning, and the FDA analysis focused in great detail on female U.S. patients and how their characteristics might explain that. And I understand, from both the Sponsor and your comments, that they are a little bit more complex.

What I wanted to get into was the other side of the coin. It may not be the patient. It may be the operator and their experience with the more complex -- was there any analysis looking at a learning curve? And the reason I introduce this is that I understood, from the timeline the Sponsor presented, that there's been a much greater presence of this device in Europe than the U.S. So were more people experienced who saw the female patients in Europe and that could explain why it benefits them but not the most complex U.S. patients, which happen to be females?

DR. ZUCKERMAN: Okay, Dr. Somberg, I'd like to just point out to the Sponsor that during this discussion period, some of the questions may be best handled by the Sponsor. Your question is an excellent one, and I hope Dr. DeFord and his team will be able to reply to you after lunch.

Thank you.

DR. PAGE: Dr. Lange.

DR. LANGE: Again, great presentations from both groups.

Thank you very much.

I want to go back to Slide 110 for just a moment. This is the U.S. females, and this is the total population. I just want to make sure. This is the total population, not the population that had an analyzable DUS, correct?

DR. JOHNSON: That's correct, Dr. Lange.

DR. LANGE: Can either you or the Sponsor provide us -- again, I'm interested in the smoking with regard to the 98 patients that are U.S. females that actually were analyzed.

DR. JOHNSON: We don't have that in slides yet. But yes, either one of us, yes.

DR. LANGE: Okay, just either one would be great. Thanks.

DR. ZUCKERMAN: Okay. And the analysis methods may be slightly different, so the Sponsor also has the opportunity to respond to that key question after lunch.

UNIDENTIFIED SPEAKER: (Off microphone.)

DR. PAGE: Yes, you may. But I'm working to try to keep track of the questions as we generate them here. So the Sponsor and FDA -- and, Bram, you're satisfied everybody understands the question, because I wanted to obviate the need to review all of the questions for after lunch at the end of this session.

DR. ZUCKERMAN: Excellent point.

Dr. Lange, could you rephrase your question?

DR. LANGE: Yes, sir. If we could show the current smokers for U.S. females that were actually analyzed with regard to their patency rates. That would be 98 females. Again, I just want to understand. The Sponsor is representing that the difference is due to smoking and the FDA feels like it's not due to smoking. Is that fair?

DR. JOHNSON: This is Terri Johnson.

My understanding is that the way the Sponsor analyzed the data is to look at the outcome results, whether the smoking has affected the outcome. The way I looked at the smoking data is whether there is a comparable proportion of smokers in both groups. So if there is any smoking effect, then it's not because we have more smokers in one test group, one group versus the other.

DR. LANGE: Thank you.

DR. PAGE: And I saw Dr. Hirshfeld and then Dr. Naftel.

DR. HIRSHFELD: Could we bring up -- I think it's Slide 102, which is the primary -- the difference in primary effectiveness between the ITT and the PP groups. And this is mainly for Dr. Johnson.

When I look at the raw rates, they're very similar. But there's been a loss of a substantial number of patients, particularly out of the PTA group, because of the -- presumably largely because of the geographic miss question, which the Sponsor has indicated that they feel is not a relevant

reason, but that's what the protocol specified. So the loss of the patients without really major changes in the rates is enough to cause this test to fail significance compared to when all the patients in the ITT group are included.

So what does this say about the robustness of the ITT inclusion when the loss of a small fraction of the total patient population seems to be enough to cause loss of significance even though the actual event rates are similar in the two populations?

DR. JOHNSON: This is Terri Johnson.

That's actually a very good question, and it's something that -- it's a big issue when we do analysis of the data. One of the reasons why we do the power calculation -- sample size calculation is so that we don't have that question. But it's inevitable. I mean, best practice would be to reduce protocol violations so that we don't have so much exclusion, and second, we have sufficient sample size.

DR. PAGE: I'm going to ask that we continue this discussion after lunch. I think it's a very important question, and I'm going to be interested in Dr. Naftel's perspective on the balance between sample size being the right size, but then when you reduce the population that's being analyzed, whether that's saying that it is not a robust finding or whether the study was sized just right, and when you cut out a certain percentage, whether that is an indictment of the results. But I'm going to put that issue on hold, and we will discuss that after lunch.

DR. JOHNSON: Yes, Dr. Naftel's comments will be very appreciated.

DR. PAGE: Yes.

DR. ZUCKERMAN: But, Dr. Page, I think you've just put the thumb on the nail. That's really a question that needs to be handled by our Panel. And when the Panel wants to blame someone, I'll be glad to participate in this very important discussion and point.

DR. PAGE: Great. And, Dr. Naftel, I had you to ask the next question, but I would emphasize, we're just looking for brief clarifying questions to the FDA now. So I'm not asking you to respond to this other issue.

Dr. Naftel.

DR. NAFTEL: So I'd like to, first of all, sincerely compliment both the Sponsor and the FDA. I think the analyses and the design are quite nice.

Having said that, there are two issues that have gone on for the last 20 years that everybody in this room knows. One is the question of outside the U.S. versus U.S. That always comes up. Always. The second thing is gender differences always comes up, and even more emphasis lately from the FDA.

So to start off and say subgroup analyses aren't really legitimate and it is ad hoc, I'd like to strenuously disagree. These should be

prespecified analyses looking at U.S. versus non-U.S. and females versus males. And I'd like to gently chide the FDA and the Sponsor. This should be built in the design of the study, even with the ultimate effect of increasing the sample size. We shouldn't have to be dissecting apologetically for these things that we knew we'd have to deal with.

Okay. Now, having said that, I have a real-life question for the FDA. So the rules are, as I understand them, for pooling, you look to see if you can pool. If you decide you can't, then you're obligated to treat it like it's two different trials, in this case, one in the U.S. and one in the outside of the U.S. So here's my question -- and I think I heard the answer. Is the FDA telling us that we can pool or we cannot pool?

DR. ZUCKERMAN: Dr. Naftel, let me take a first crack at that. I think you've heard a variety of opinions from the FDA. Dr. Johnson is a frequentist statistician, and her comments were no. Ms. Pack's comments were more guarded because pooling is an issue that includes both clinical and statistical considerations. So, again, I think that Dr. Johnson may just want to affirm her statistical input. But the FDA, in the spirit of full disclosure, indicated that this is a complex issue and that we really need a panel of clinical experts and you this afternoon to fully delve into this topic with my help.

Thank you.

DR. PAGE: I have Dr. Slotwiner and Dr. Cigarroa and then

Dr. Posner.

DR. SLOTWINER: Thank you.

I wanted to ask two questions related to Slide 35, about possible treatment bias. And so the questions are, are these -- so the first question is, is this a necessary difference, the different inflation pressures, shorter times, and the geographic miss? Is that part of the difference in the actual different -- in the DCB versus control? And since the treatment balloon appears different, is there a way to avoid the operator having this knowledge of which treatment a patient is getting?

DR. PAGE: Dr. Slotwiner, I might save that question for the Panel discussion. I'm not sure FDA is going to be able to comment on the nuances between the clinical decision of one balloon versus another and how those were implemented, unless I'm missing something here.

DR. SLOTWINER: No, I guess that makes sense. I'm just curious how the study could have been designed to not have these obvious differences and if there's a way to avoid that type of bias.

DR. PAGE: Yes, I think that's going to be a conjecture that we'll want to discuss as a Panel.

DR. SLOTWINER: Okay.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: So with regards to sex differences by geography and the distinction between outside of U.S. and U.S. efficacy or

lack of efficacy, I'd like to know whether or not any data exists on differences in the age or the comorbidities associated with women outside of the U.S. versus within the U.S. There certainly have been differences in prior trials. And women in particular, irrespective to men, tend to present later and tend to have more extensive disease and, even when vessels remain patent, tend to complain of more claudication.

So I think that understanding the drivers of target lesion revascularization in women and understanding differences in the characteristics -- or the potential for differences -- would be important to help me continue to gain better understanding of the differences in performance.

MS. PACK: So with regards to age and other covariates, those were certainly included in the analyses, and I think that we can present that probably after the break.

DR. JOHNSON: I just need one clarification. You would like to see them for -- break it down to geography and gender. For example, OUS female, OUS male, U.S. female, and U.S. male.

DR. CIGARROA: I'd like the specific focus stratified by out of U.S./U.S. for women in particular, with regards to baseline demographics, angiographic data, and drivers of target lesion revascularization. And so it may be that there are differences in the U.S. in terms of the threshold for a provider to revascularize somebody who may have a stenosis of 55% or 60%.

We know women complain of more claudication, independent of the percent residual stenosis.

MS. PACK: I think that second part will have to be something done by the Sponsor.

DR. ZUCKERMAN: Dr. Cigarroa, let me ask if this is something reasonable that the Sponsor can do. One is to do the analysis that you requested for this trial, but I think we need to recognize that the sample size is modest at best. And perhaps it would also be helpful, if you're in agreement, that the Sponsor gives us a summary of the peripheral data for possible gender differences in this area, to put it into context, because this is a very unusual result. Certainly when the FDA has reviewed the literature, we've not seen these findings previously replicated.

DR. CIGARROA: Dr. Zuckerman, the point regarding the differential impact on out of U.S. versus U.S. with regards to gender not replicated in other trials, I'm just a bit confused.

DR. ZUCKERMAN: I'd like Dr. Buckley to respond to that. She's done a rather extensive literature review and hasn't found that gender has a major impact on PTA results in this particular vascular bed.

But, Dr. Buckley, do you want to briefly summarize?

DR. BUCKLEY: Well, I think there is information with regard to male and female from multiple studies looking at gender differences where women may be older or might have more chronic limb ischemia, et cetera, as

a group compared to their male cohorts.

I think what's of particular interest in this study isn't so much the male/female differential. It's that the women, as an overall group, performed better with the control treatment than with the drug-coated balloon. The men had a benefit. Their difference was an average of 22.2% benefit with the balloon -- with the drug-coated balloon, whereas the women, as a group, actually had almost a 5% benefit in favor of the control device. So that's one of the aspects that we were struggling with and would like your input on.

DR. PAGE: So, Dr. Zuckerman, do we have further data analysis there that you want to summarize now in terms of the work for after lunch for both the FDA and the Sponsor?

DR. ZUCKERMAN: I think the Sponsor may want to add to their general literature review of gender effects and PTA treatment in the femoral bed.

Thank you.

DR. PAGE: Thank you.

Dr. Posner, I haven't forgotten about you. Dr. Ohman's on the phone and has wired in that he'd like to be called upon.

Dr. Ohman.

DR. OHMAN: Thank you, Dr. Page.

My question for the FDA, if you can hear me --

MS. PACK: Yes, we can hear you.

DR. PAGE: Yes, we can hear you well.

DR. OHMAN: -- is have you examined age, independent of women or men, just the factor of age and what impact that has on the efficacy results?

MS. PACK: Yes, we have.

Dr. Johnson, would you like to speak to that?

DR. JOHNSON: Not just the FDA. I believe the Sponsor has included that in the PMA report already, that age was not a significant factor or it was not significantly different between the test device and the control device group.

DR. OHMAN: So if I can follow on with a second question to that, Dr. Page.

Would that indicate that the "funny" response in women is driven by the response in younger women?

DR. BUCKLEY: This is Donna Buckley.

Can you rephrase that again and repeat the question?

DR. OHMAN: So the follow-up question would be, would this mean that the "unusual" results are reflected by the outcomes in younger women?

DR. JOHNSON: This is Terri Johnson.

When I looked at the mean age of U.S. females in the test

device group and control device group, actually there were 71 and 72, respectively. So at least there was no statistically significant difference. So I do not believe that age was the influential factor in the patency rate.

DR. OHMAN: Okay, thank you.

DR. PAGE: Thank you.

Dr. Posner.

DR. POSNER: Yes. Dr. Cigarroa anticipated a lot of my questions, but it's basically all women are not created equal. And particularly in the age group that were used in this study, because they lived through the hormone replacement therapy, and the question is, has there been analysis of how many of the women in this study were on hormone replacement therapy, continue to be on hormone replacement therapy, and the time involved? Because clearly there is a cardiovascular impact of that. If they're continuing on replacement or if they're on replacement shortly after menopause or for a longer period of time, it's going to be an effect on smooth muscle.

The other question I have is one of vessel volume that was asked a little bit earlier. Clearly, at this age, the female vessels are probably a little bit smaller, and so the percentage change for a small millimeter difference in growth is going to be a larger percentage change. And I think, again, that question was asked earlier, and we ought to get that answer this afternoon, of real numbers in millimeters and centimeters rather than just

percentages, to see whether that changes the statistics.

And then the last question I have for females is the claudication that's seen post-treatment. Is that definitely due to increased muscle mass or ischemia due to that? Or is there some spasm involved? Because, again, women tend to be prone at that age to more vascular spasm.

DR. ZUCKERMAN: Okay, Dr. Posner, you've posed a fascinating set of gender issues and questions. I'd like the Sponsor, this afternoon, to give us their complete dataset regarding covariates that were measured and any important differences that they've seen.

But I suspect that a lot of the information that you're looking for is unknown and that's why, in general, I would just ask the Panel to consider that when we're doing the subgroup analyses of moderate sample size, the benefits of randomization may be lost. We have a lot of unknown covariates, as you were pointing out, that were not captured. And although, as Dr. Naftel indicates, it is very important to look at these analyses, we need to look at them in the right interpretative light.

Thank you.

DR. PAGE: So just so I'm keeping track of what we're asking the Sponsor for, we're asking for you to give us the analysis, as fully as you can, in terms of women who received these therapies and to tell us what you did and didn't measure. And I think that will be very helpful.

Dr. Lange.

DR. LANGE: I'm going to ask for help from our statisticians. Now, keep in mind, this is the guy that can't count above 4 to get to 5, okay? But I want to take a look at two slides and see -- Slide 100 and then Slide 92. Okay. And just to draw your attention to the bottom line, for the people that were excluded -- and the primary exclusion again was because of geographic miss -- there's a much bigger difference in terms of the effectiveness.

Now, let's go to Slide 92 for a second. That slide. And it looks like the geographic miss was much greater in non-U.S. sites than in the U.S. sites. There's a 25% difference in the non-U.S. sites and just a 7% or 8% difference in the U.S. sites.

So did you all do an analysis to see whether this accounts for the difference between U.S. and non-U.S.? I mean, on the one hand we're saying that geographic miss doesn't really matter. But is there an interaction between the geographic miss and the U.S. versus non-U.S. differences?

DR. ZUCKERMAN: You know, from the FDA perspective, this is exactly why we put in these slides, Dr. Lange. So you're counting very well and you're understanding the data. Again, we've asked the Sponsor to carefully think about a response to this critical issue, and after lunch, I know that they're prepared and Dr. DeFord will ask the right people to speak.

DR. LANGE: Terrific. And the question was to be answered after lunch, but just to pose it now.

Thank you.

DR. PAGE: Dr. Simon.

DR. SIMON: Thank you.

This is just, again, sort of a follow-up to some of the other questions. If we could go back to Slide -- I think it's 99 or 100. I have to get that myself. Slide 100. And it touches on sort of the robustness of the data question.

But do you think, Dr. Johnson, you could just provide for us -- since this geographic miss issue has become very relevant, if we were to try to back into a p-value of 0.05% on this slide, that is, we went from 12.6 to 9.3 and we lost, by your calculation that becomes a p-value of 0.11. And I'm just wondering, if you were to try to reverse engineer a p-value of 0.05, how many patients would you have to add back into the control PTA, keeping us at 56? I mean, it seems like you would only need to add in very few patients to end up with a significant p-value; am I correct?

DR. JOHNSON: Yes, you're correct. So I think it is in the Panel Pack folder. We performed tipping point analyses --

DR. SIMON: Right.

DR. JOHNSON: -- for the missing data. And if you look at the per-protocol analysis for the tipping point analysis, you would see the observed rate is very close to the border where the objective will be met versus objective would not be met. You're correct.

DR. SIMON: Do you think you could just provide -- because at

some point I kind of get lost in percentages. And so when you say -- just to put it into context, to simply say, if you put five patients back in or four or three, you're at significance. You know, I don't have the tipping --

DR. ZUCKERMAN: Okay, Dr. Simon, we will commit to doing that analysis.

DR. SIMON: Yeah, if you could provide that.

DR. ZUCKERMAN: And the other thing that you should look at is just the 95% confidence interval from -2.1% to 20.7%. It, again, is very close to zero and supports your analysis, but we'll give you the numbers.

DR. PAGE: I have a brief question. I sense some frustration on the part of the FDA, in terms of what appears to have been an agreement -- and this is what I want clarification on -- as to what number of 12-month follow-up safety data patients -- what number of patients with 12-month safety data would be available at the time of PMA.

I'll ask. Was there a tacit agreement with the Sponsor that that would be available at the time of PMA? Because I sense there's frustration that it actually was that the PMA was filed prematurely, at least in terms of the FDA's perspective. And I ask this from the standpoint as a Panelist. We need to respect what was decided between the Sponsor and the FDA. For example, what is the primary endpoint? What will that look like? And perhaps we'll have the Sponsor answer during the Panel deliberation after lunch.

But from FDA's perspective, was there an agreement that a certain number would be provided and the fact that you were surprised when that number was not there in the -- when the PMA was actually filed?

MS. PACK: Yes, I actually have a backup slide for this that I can pull up. So, yes, from FDA's perspective, we felt there was agreement that there would be a minimum of 100 patients at six months follow-up data provided at the time of the initial PMA submission, as well as a minimum of 50% of the 12-month follow-up data provided at the time of the initial submission. We felt that because they had quite a good rate of enrollment, that allowing that and then factoring in the time for the review, by the time we got to panel, we would then be able to have a majority of the data available prior to Panel presentation.

However, as we've stated, at the time of the initial submission, there was actually even less than what we've presented here today, and now what we have is approximately 55% of the data has been provided out of the 1,029 that have been enrolled.

DR. PAGE: And that's 55% of the number that you were anticipating to have at the time of PMA.

MS. PACK: So we didn't specify what the denominator needed to be. The Sponsor had come up with 869, I believe, as their required sample size from their statistical perspective and that then, with a 15% lost to follow-up, came out to 1,022. They enrolled 1,029. So we didn't specify specifically

what that number needed to be. Instead we gave a percentage.

DR. PAGE: Okay, thank you.

Dr. Lange.

DR. LANGE: Is the data that's provided, has it been adjudicated or not?

MS. PACK: Yes.

DR. LANGE: Thank you.

DR. PAGE: We're nearing the lunch hour.

Dr. Thuramalla.

And I do want to make sure that our Industry Representative, our Patient Representative, and our public representative have all had a chance to ask questions if they wish.

So please proceed.

MR. THURAMALLA: Thank you.

To understand the gender impact in a little bit more detail, I have two very brief questions. What is the impact of the mean age between the genders? Was there any difference between the age studied between females and males?

The same question in terms of sample size. From Slide 67 of the FDA, I see that the number of patients studied among the females is a smaller sample compared to the male population studied. Would that have an impact or help us better understand the gender differences we're

noticing?

Thank you.

DR. BUCKLEY: To your second question, I think approximately a third of the patients were female and two-thirds were male enrolled in the overall trial.

To the first question, in terms of differences of ages between the men and women, we can pull that up. Do you have that available?

DR. JOHNSON: I don't have that available for overall OUS and U.S. male and female, but I do have them for U.S. male and female. The U.S. male mean age was 66.5 for test Lutonix DCB and 67.7 for control PTA. And I believe for U.S. female it was 71.3 for test Lutonix, 72.0 for control PTA.

DR. PAGE: Thank you.

Ms. Chauhan, did you have any further questions?

MS. CHAUHAN: Dr. Cigarroa asked most of mine, but this brings up one. In the population, what is the relative incidence of male and female? Is it what's reflected here or is it different?

DR. BUCKLEY: This enrollment of male and female is somewhat typical in these kinds of endovascular trials.

MS. CHAUHAN: Of the trial, but what about of the population?

DR. BUCKLEY: Yes. I mean, I think that's one criticism that some have levied, that these endovascular trials may not enroll an adequate number of female patients to truly reflect the overall disease.

DR. JOHNSON: This is Terri Johnson.

And I think that's very well reflected from Dr. Naftel's comments, that since the study is not designed to analyze separately for male and female, that we may probably not have enough patients in female.

DR. PAGE: Thank you.

Dr. Hirshfeld has one clarifying question.

DR. HIRSHFELD: Yes. This just has to do with the way that the discussion will go this afternoon, because I think a lot of the questions surround the magnitude of the effect size. And all of the statistics that we've seen so far have been binary statistics, and restenosis is not a binary problem. And, in fact, many coronary restenosis trials use cumulative frequency curves as an assessment of the magnitude of the impact of a particular intervention intended to prevent restenosis, and we haven't seen anything quite like that. And the closest thing that we've seen is the Sponsor's Table 16, where they stratify event rates by peak systolic velocity ratio categories or cumulative categories.

I don't know whether the Sponsor has access to the software to do quick cumulative frequency curves on short notice, but I think that something of this nature to get away from binary statistics would be useful.

DR. ZUCKERMAN: Great. So, Dr. Hirshfeld, the Sponsor has done CFD curves on their core lab data beforehand, and they will try to respond to your questions so that we'll see more of a continuous analysis for

relevant variables.

DR. HIRSHFELD: Great.

DR. PAGE: Okay, I think it's now time for us to break for lunch.

Panel members, please do not discuss the meeting topic during lunch among yourselves or with any member of the audience. We will reconvene in this room exactly one hour from now at 1:00. Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

Did you have a comment, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, for Panel members. It's extremely important, as Dr. Page has mentioned, that you take a timeout and not discuss Panel issues.

Secondly, there is a special lunch room for Panel members. I believe it's the Maple Room, Jamie.

DR. PAGE: Great, thank you.

With that, we are adjourned until one o'clock.

(Whereupon, at 12:00 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

DR. PAGE: It is now one o'clock, and I'd like to resume this Panel meeting.

We'll now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose

not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you very much.

We've received six requests to speak. Each person will have five minutes to speak. I can see the little lights there. I just want to confirm. It's a five-minute total timer, and there's a one-minute warning. So don't start it yet, because they aren't up yet, but thank you. So it will be green for four, yellow for one, and then at red I will ask for the speaker to wrap up so we have time for everyone to speak. When you speak, please speak clearly into the microphone to allow the transcriptionist to provide an accurate recording of this meeting.

Our first speaker is Dr. Alan Block.

Welcome, Dr. Block.

DR. BLOCK: Good afternoon. Just to let you know, I am being financially reimbursed for transportation but have no relations with Bard other than that.

I am a podiatrist at The Ohio State University.

DR. PAGE: I hate to cut you off. I'm not seeing a green light yet.

DR. BLOCK: Perfect. All right.

DR. PAGE: Thank you.

DR. BLOCK: Sorry about that.

My transportation is being taken care of by the Sponsor. I have no financial relationship with them other than that. I am here for My Leg, My Choice.

I'd just like to bring up why I'm in favor of what we've seen in the protocol here for the drug-eluting stent. I am a podiatrist. There are 180,000 amputations that happen here in the United States a year. By the way, it's about 3:1 men to women, as far as amputations. It may be time to treat that brings that on. We can't really answer that right now, but the important part is what's going on.

And 12 years ago, when I was brought into this field of revascularization, it was engineering and it was thinking that brought us to the point we are now, that we can have a drug-eluting stent. In 1978 John Simpson does a balloon angioplasty of the heart and it's ridiculed, and now it's the gold standard.

But I will tell you, as a treating physician, the ability of critical limb ischemia for me to treat has passed monumentally. At the beginning we were just hoping to make it to the knee and now we can go to the foot. And we need these.

Now, I work in a large hospital that has a very large cancer hospital attached to it, and when you look at this, when you look at paclitaxel, it's used for breast cancer. And not many men, about 3% to 5% of the men, come up with breast cancer. So you're looking at this, and it

happens to young vital women who have not gone through menopause at this part.

But the point is this: We do have protocols and we need to go forward because evolution is really important to going forward.

You know, I have in my own practice adopted the protocols of the cancer centers, of looking back and checking on these patients and following them, and following them by a three-month period. And this is where this device comes in, because we have gotten down to the point where we've stented and we've ballooned and we've atherectomized, but we need to start treating the vessel because we have to start looking for different ways because patency rates are critical.

Patency rate is, very simply, when you looked up on that thing, it may be just a scribble on a line or a Kaplan-Meier curve to you, but it's a patient's life to me. And I'm the guy sitting there holding their hands when I have to take something off. And we know, once a patient loses their below-knee amputation, only 50% of them will ever walk again. And if it's above-knee, only 75% of those patients will never walk again.

The economic impact in the state of Ohio is incredible because it's about $50,000 to do the amputation, and to keep that patient in an extended care facility for a year is $107,000. The drain on the medical system from these patients is incredible, if we can keep them patent, if we can keep them open. I really believe the future is going to be genomic medicine with

this and treating the blood vessel and not just treating the plaque. And, unfortunately, not all plaque is the same. And I don't think just all medication or mechanical treatment is going to be enough, but it's going to be a combination.

The other point, really very simply, 80% of diabetics -- you find out that the patient is put in the hospital. Eighty percent of diabetics are hospitalized for diabetic foot infections, and 85% of diabetic amputations are occurring preceded by an ulcer. That's pretty impressive when you start to hear that. Thirty-one percent of their wounds heal -- because we're not providing adequate circulation or keeping the circulation open long enough. So, again, it's important to me that there has to be a treatment for the intima of the artery, as well.

Very simply, if you look at the biggest growing population in the United States, it is 85-plus at this point, and we're living sicker and longer, unfortunately. When you start to look at that, we realize there are three buckets of patients. There are patients who are diabetic, renal disease, and age, and we're finding these people need more treatment longer.

This is a very slow progressing disease, and by the time we're aware of it, the problem is we're looking at treating patients who have claudication that go to critical limb ischemia because they weren't aware or didn't seek help soon enough. So it's more important that this awareness happens. And it's more important that we start to treat these people outside

the box that we usually do treat them.

So, very simply, when you look at Rutherford -- and I know that you were talking about Rutherford today, the Rutherford score. When you treat ulcers, if you read the original paper by Rutherford, it's interesting, he never meant to include diabetics, and that's the score we use. But, again, I'm looking for patency, and I'm looking for long-term, no critical limb ischemia. And these are the most important things. And this is the future, and this is where I think devices, like what we're talking about today, go.

So with that, I'm going to wrap up, and I thank you for your time.

DR. PAGE: Thank you, sir.

Our next speaker is Dr. Eric Peden, who is also going to be speaking on behalf of Dr. Carlos Mena and Dr. Mahmood Razavi.

Dr. Peden.

DR. PEDEN: Hi. Thank you very much for this opportunity. My name is Eric Peden, and I am a vascular surgeon in Houston, Texas, where I'm Chief of the Division of Vascular Surgery at Houston Methodist and the medical center.

I do have several disclosures. Importantly, I do have a consulting relationship with Bard. My travel costs have been covered by Bard Lutonix to come to this meeting. I have never used this device. I was not part of the original trial. And as a surgeon, I have some gross slides, so I apologize

to those of you who had a queasy stomach and a full lunch.

Vascular surgery. We really embrace this group of patients. We think it's really a big part of our practice, and we get involved in all aspects of that, from conservative management, to medical therapy, to endovascular treatments, and then ultimately to surgery and sometimes the termination of the limb.

Peripheral arterial disease, as we've heard, hits millions of Americans, and fortunately most asymptomatic. But the claudicants, minor tissue loss, and major gangrene are patients that we get involved with frequently in our management. And sadly, although amputations are on the fall, they are still very prevalent. In our own hospital, which is a big hospital -- we're located in Texas, as I said, one of the areas that still has a very high prevalence of amputations, and our facility does about 1,000 at the hospital, and one to two limbs every week are amputated, largely the result of peripheral arterial disease.

So lots of medical treatments, angioplasty, et cetera, that we've talked about. I'll go through those briefly.

The real mainstay for these patients is medical therapy of their comorbidities, because we know most of these people are going to die of heart disease and strokes, and we want to keep their limbs attached and keep them as healthy as we can. Pletal we do use liberally, but there is no medicine that's going to take that lesion away that's blocking off the

femoropopliteal segment. Sadly, we're just not there yet.

Endovascular therapy is clearly the dominant treatment of choice even for surgeons like myself and the current generation. Probably about 80% of what we do is endovascular rather than open surgery.

Angioplasty, as we've heard, has relatively poor patencies.

Stenting, as we know, has problems with fractures and restenosis, as we see. And for me, as a surgeon, sometimes that takes away my next option for these patients, which is a real problem.

Atherectomy is not clearly shown to be any better than the other treatments, and sadly, sometimes it's associated with embolic events and complications, like we see the black toes to the right.

Surgery we think of as kind of a big stick that we carry that can give people the most vascular supply in their foot again, but sadly also comes with the biggest cost because of the prolonged hospital stay and prolonged recovery afterwards, morbidity of wound complications like you're seeing on the screen, and occasionally mortality.

Angiogenesis we're very excited about, but it really has not made it out of the clinical trial arena yet, and it's not mainstay therapy.

So lots of needs for these patients because we're fighting atherosclerosis, which is essentially like fighting the nature of vascular disease. Our patients are going to have failures of their treatments. None of these things are a cure. None will last forever. We need safe, effective

treatments that hopefully will be more durable.

From my own perspective, we need to leave our next options open for us, and frequently we think that is not leaving metal behind, if we can. We're really intrigued by this concept of being able to move beyond just a mechanical treatment and add biology to hit this disease from both perspectives. We're hopeful about the original results, as we've heard, and we'll see, as time goes on, that hopefully we'll find out which exact patients will benefit from this.

Thank you.

DR. PAGE: Thank you very much. Did you have other statements to present on behalf of the other two physicians?

DR. PEDEN: I do. I've been asked --

DR. PAGE: We'll start the clock again for you.

DR. PEDEN: Fantastic. I am reading the statement from Dr. Mahmood Razavi, who unfortunately has a scheduling conflict and could not make it today.

"Good afternoon, Dr. Yancy, members of the Circulatory System Devices Panel, FDA officials, and others. My name is Mahmood Razavi. I thank you for the opportunity to speak with you today and let you know that I support the use of the Lutonix drug-coated balloon among PAD patients in the United States and to share with you the reasons for that support.

"I am a board certified interventional radiologist with over 20 years of experience in treating patients with vascular disease. My current position is the Director of the Center for Clinical Trials and Research at the St. Joseph Vascular Institute. I have served on editorial boards of several scientific journals and have been the editor of *Techniques in Vascular Interventional Radiology*. I was also an investigator in the LEVANT 2 trial.

"Endovascular, first, is now the dominant therapeutic strategy in patients with both intermittent claudication and CLI in the western world. Yet much improvement is still needed in treatment of vascular segments such as the femoropopliteal. It is clear that improvements in this area will come in stepwise fashion. When new technologies or approaches show a better outcome in prospective randomized trials, it behooves us to be able to offer it to our patients. The Lutonix DCB is one such technology. The data presented here and my experience as an investigator is why I believe Lutonix DCB is an appropriate first-line treatment for patients with lifestyle-limiting claudication. It offers superior patency to PTA alone, with strong safety.

"PAD patients already have many treatment options. Many are unproved and most have limitations. As physicians, we need proven treatment options for this diverse and growing patient population. Making the Lutonix DCB available to patients here just makes sense.

"Thank you for your time and consideration of my experience with the device."

DR. PAGE: Thank you very much. Did you also have a statement from Dr. Mena?

DR. PEDEN: Yes. The same scenario.

"Good afternoon." Unfortunately Dr. Mena was tied up by a family emergency.

"My name is Carlos Mena, and I'm pleased to be here to discuss the successful outcomes I achieved as an investigator during LEVANT 2 for the Lutonix drug-coated balloon and why I believe this technology is an important additional tool patients and their providers need.

"I am an Assistant Professor of Medicine and the Medical Director of Vascular Medicine at Yale-New Haven Hospital. I am board certified in internal medicine and cardiovascular disease, and I have a clinical interest in advanced endovascular therapy for peripheral vascular disease. As such and as mentioned, I was an investigator in the LEVANT 2, the trial being discussed today.

"My patients range in age from 60 to 80 years old. By and large, they were relatively active until their PAD symptoms began limiting their lifestyles and their ability to maintain their usual family obligations. Their disease disrupted their lives and caused them considerable discomfort and pain.

"I'm amongst the most experienced clinicians with this device in the United States. My experience with Lutonix DCB highlighted to me that

U.S. patients should also have this technology available. I encountered no safety signals with this device, and my patients achieved benefits: durable patency. This is an important outcome, since it translates to improved mobility and lessened pain. These are the two outcomes my patients are desperate for and seek treatment to achieve.

"Based on my experience, I see no reason why the Lutonix DCB should not be available to providers when treating PAD patients. It is an established technology that utilizes an approved prescription drug. It has a history of safe use in Europe. My own extensive experience reinforces its safety and benefits to both men and women with PAD. Clinicians need more tools, and the growing number of patients with PAD need more treatment options. The Lutonix DCB fulfills these needs.

"I'd like to thank the FDA for allowing me to speak to you today, and I'd like to thank this Committee for its attention."

DR. PAGE: Thank you very much, Dr. Peden.

Our next three speakers are patients. The first is William Race.

Mr. Race, welcome, sir.

MR. RACE: Good afternoon, ladies and gentlemen. It is with great humbleness and appreciation that I stand before you this day, as I never felt that I would be called to testify before this Panel.

I am a diabetic, severe, they say. But six years ago I was suffering from peripheral artery disease. It was all I could do to walk a block,

let alone walk for enjoyment. My doctor, Jihad Mustapha, endeavored to alleviate the problem by operating and opening the blood vessel by cleaning it out to the best of his abilities. This was done on October 19th, 2008, on the left leg. On October 27th, 2008, he performed the same surgery on the right leg. This was successful for a short period of time, but soon returned. He went in again on the right leg and placed a stent in the artery.

After a short time the left leg became blocked as plaque continued to build up in the blood vessels. We were uncertain of how to proceed in order to do away this problem. I continued to walk as best I could. But the pain became so bad that wherever I went, I used an electric cart if one was available.

In 2012 I received a phone call wanting to know if I'd be willing to participate in a research program seeking to achieve a solution for PAD. The program was presented to me, providing an overview of all of the procedures. After some deliberation, I accepted the invitation because I felt it would benefit me as well as have the potential to help thousands of others who suffer from the same issue. Everyone deserves a means of overcoming the same debilitating issue of PAD.

So as I stand here, I beg this Panel to pass this reform for the use of this procedure. It helped me, and I have been able to walk pain free for a year and a half. What a joy.

This is not to say that it is all Dr. Mustapha's doing, because I

am born-again believer in Jesus Christ, and many people were praying for me and for this surgery. They also prayed for wisdom for Dr. Mustapha as he did the surgery on the left leg, as the right one was not being a problem at this time.

Due to the great strides made in medical research, I have now lived longer than either of my parents did. They both had cardiac disease that today may very well have been corrected. In my opinion, had this surgery not been granted as a research project, I would still be suffering from pain from closed arteries, possibly even having to have more severe surgery than a mere intervention of the leg.

Again, ladies and gentlemen, this research project, in my opinion, has been a great success, and I feel the need for it to be established for the benefit of all.

Thank you for your attention and for allowing me this time to address this issue.

DR. PAGE: Thank you very much, sir.

Our next speaker is Terrence Hoover.

Welcome, Mr. Hoover. I understand you're going to be speaking on your own behalf and that of Michael Perl; is that correct, sir?

DR. HOOVER: That's correct.

DR. PAGE: Great. Please proceed.

DR. HOOVER: Good afternoon. My name is Terry Hoover. I'm

79 years old, and I am a retired pediatric dentist. I live in southern Maryland with my wife and daughter. And in support of transparency, I want to say that Bard has reimbursed me for my travel to be here with you today.

I was a patient in the study being discussed here today, and based on that experience, I support it being made available to other patients, as well. I was in pain when I entered the study, following a previous procedure that proved to be ineffective. Since being treated with a device, this device, more than two and a half years ago, I have been pain free and able to return to my normal activities.

I'd like to begin by offering a brief family health history, which I hope will point the way to how I became part of this study.

My father passed away at age 72, having lived with the effects of significant atherosclerosis and its symptoms for the last 20 years of his life. For him it began with angina at age 52, subsequently resulted in mitral valve surgery, and also an abdominal aortic aneurysm requiring resection and graft. In addition, for the last two years or so of his life, he experienced increasing discomfort and decreasing mobility in both legs, again attributed to the narrowing of the major arteries in his lower extremities. This had a significant impact on his ability to maintain his normal and healthy routines, and he subsequently passed away as a result of a sudden and massive heart attack.

I personally became aware of my possible involvement with

atherosclerosis at age 72. I had been taking a statin for several years in an attempt to lower my blood pressure -- excuse me -- lower my blood cholesterol levels to a more acceptable range. However, in December of 2007, at age 72, I sought an appointment with my primary care physician after experiencing weakness and extreme fatigue following a period of moderate exercise. Clinically he found an abdominal aortic aneurysm. I was referred to a vascular surgeon to confirm the diagnosis. In addition, he also discovered blockage of my right carotid artery. And both findings needed to be surgically treated as soon as it could be arranged.

However, a cardiac workup was needed to be done prior to these procedures, and in short, they found evidence that four of my coronary arteries were blocked in some fashion, and an open heart quadruple bypass procedure was done. Three weeks following that, I returned for a resection of the aneurysm and an endarterectomy of the right carotid artery.

Following that, my life was pain free with no limitations for the next three years. Then, in late September of 2011, while I was taking our family dog for his daily walk, I began to experience ever-increasing pain in the calf of my right leg. Over a period of several weeks the pain became severe enough that after walking a block or two, I had to stop and rest for several minutes. It had become a problem.

I first met Dr. Bernado when I was referred to Washington Hospital Center, and he confirmed the diagnosis of arterial blockage, and I

was treated with a traditional angioplasty surgery and was discharged home. I experienced immediate relief following this procedure and was able to resume my normal activities comfortably. Then, in approximately three months, the discomfort recurred in my right calf and in a short time required a repeat visit, to visit Washington Hospital Center.

At this visit, Dr. Bernado informed me of this proposed study. I agreed to participate in this study, and in November of 2011, two and a half years ago, I underwent the revised angioplasty procedure with a paclitaxel-treated balloon. Since then I've had no pain or physical limitations, and I'm able to enjoy my normal activities with comfort.

Thank you for letting me provide my perspective today regarding this procedure, which has been a wonderful help to me.

DR. PAGE: Thank you, sir. Are you also going to be speaking on behalf of Michael Perl?

DR. HOOVER: I am.

DR. PAGE: Okay, we'll reset the clock for you.

DR. HOOVER: All right. Dr. Perl is unable to be here in person due to a family illness, so I will try to read his prepared testimony on his behalf the best I can.

"First of all, I'd like to thank the Committee for allowing me to testify in this way. Unfortunately I've had problems with my family, with some cancer surgery, not myself, but my daughter-in-law, which precludes

me from coming to Washington to see you at this time.

"But a little bit about myself. My name is Dr. Michael Perl. I've been a dentist, a periodontist, since 1964 and I am now retired for about six years and living the good life, so to speak. I had been in good health until one day, all of a sudden, I almost could not walk on one leg. It was causing me a lot of pain.

"I went to see a doctor, and the doctor told me that I had peripheral vascular disease in my right leg. He suggested doing balloon therapy with the medication on the outside that's being used in Europe. I was comfortable going along with the test.

"The procedure took less than an hour. I was in Yale-New Haven Hospital for possibly 14 to 16 hours. I had absolutely no pain and have had no pain since, and that was done about 13 months ago. I'm 100% satisfied and have no aftereffects from surgery. As far as I'm concerned, it's a wonderful procedure, and I'm tickled to death that everything is fine at this point, more than a year later.

"I would be glad to answer any questions you may have in the future. Thank you for allowing me to discuss this with you."

DR. PAGE: Thank you very much, Mr. Hoover.

Does anyone else wish to address the Panel at this time? If so, please come forward to the lectern and state your name, affiliation, and indicate your financial interest, if you will.

(No response.)

DR. PAGE: I'm seeing no one coming forward.

Does the Panel have any questions for the Open Public Hearing speakers?

(No response.)

DR. PAGE: Seeing none, I will pronounce this portion of the Open Public Hearing to be officially closed.

I want to thank the speakers. I want to especially thank the patient representatives. It's very valuable to us, as a Panel, to hear your own personal perspective. And I assure you, whether or not we vote favorably or unfavorably with this device, we are seriously considering your input, and we really appreciate your addressing the Panel today.

We'll now proceed with today's agenda. We're going into the portion of the open Panel deliberations. Although this portion is open to public observers, public attendees may not participate except specifically at the request of the Panel Chair.

In addition, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

At this time I'd like to ask Dr. DeFord to come forward. He and his group have been working diligently over the lunch break to address the questions. Rather than our repeating the questions, he's going to go ahead

and repeat them as best he understood and present his responses to these questions. And as needed, we'll comment or add further questions. But, otherwise, I'm looking forward to his going ahead and proceeding through the questions that we, as a Panel, asked for the Sponsor to address over lunch.

DR. DeFORD: Would the FDA mind if we put this laptop underneath? No? Okay, that's fine. You do mind or you do not mind? I'm sorry.

DR. ZUCKERMAN: That's fine.

(Laughter.)

DR. DeFORD: Okay, thank you. I wasn't quite sure there.

So John DeFord.

You did a nice job of giving our team quite a bit of homework, and we'll do the best to work through these. So we captured 21 questions that we will try to answer, and we'll try to walk right through those.

Before I start, though, I do want to just first say that I think there was a certain amount of deliberation around the amount of safety data that we provided, and I want to inform the Panel that there was certainly no intent on behalf of the company to not provide FDA what they wanted. I think there's a legitimate area of confusion here that existed, and we also believe, however, that the data we've provided is sufficient for this analysis.

I would like just very briefly to have Chris Mullin come and

discuss some of the analysis that we've done on rare adverse events and the amount of data that we have available.

MR. MULLIN: Chris Mullin.

I think we have a slide to pull up here.

DR. DeFORD: Is that CO-113?

MR. MULLIN: CO-113. Okay. So I think, as was discussed, there were certain plans for the submission of additional data to characterize safety for this device. And I think, as Dr. DeFord noted, there was some confusion about what exactly the parameters were around that. But what was submitted, I think, was well beyond what was expected in terms of demonstrating safety.

So, for example, this slide shows, among the 1,029 drug-coated balloon patients enrolled, there were zero unanticipated adverse events observed. And then by time you can see the number of patients followed, along with the upper confidence bound for that observation of zero events. And so for example, at 12 months, we have an upper bound of 0.69, well below the parameters that were discussed in terms of characterizing safety ahead of time.

And then, just specifically to the point on one particular event of interest, target vessel thrombosis. That was observed with the rate of 0.18%, corresponding upper bound of 0.99%, again, well below the prespecified target of 1.8. This is the reason we felt that this data provided a

reasonable assurance of safety.

DR. PAGE: I appreciate that.

Dr. DeFord, if I may just ask the question that I told you I would be asking. From the Sponsor's perspective, was it clear what was asked of the Sponsor in terms of the number of follow-up at 12 months, and were you aware that you were short of that, and did you nevertheless proceed with the PMA? And was there consideration of, at that time, addressing the fact that, arguably, you have very good safety data but you had not met the prespecified expectation for submission of the PMA?

DR. DeFORD: We did not. Again, there was certainly confusion. There had been discussion. The numbers weren't exactly specific. We had discussed back and forth and had submitted with the expectation that we would provide additional data ongoing. And as the review process continued and as Ms. Pack mentioned, then there became a discussion around this issue. At that time, though, I felt like and I think the Sponsor felt like we collectively agreed that we would provide additional information as it was available, but we didn't have the understanding that this was a real contentious issue for the FDA and a big concern. Again, we certainly are committed to providing them anything that they need.

DR. PAGE: Thank you.

DR. DeFORD: Okay, moving on. I have two questions, one by Dr. Zuckerman and one by Dr. Hirshfeld, that were really similar questions.

So I'm going to attempt to pool them together. And this was speaking specifically about the robust results of PSVR and cumulative frequency curve or other information that we might have to discuss the robustness of using duplex ultrasound as a measure. And I'd like to ask Dr. Jaff to come forward to discuss that a little bit. And if we could pull up for Dr. Jaff Slide AA-2, please.

DR. JAFF: Michael Jaff.

This slide that you see demonstrates the results of primary patency at 12 months, using three different duplex ultrasound PSVR cutoffs: 2.0 or greater, 2.5 or greater, or 3.0 or greater. You'll notice that each one has their merits, but clearly the 2.5 or greater, which is the one that was originally agreed to for this trial, showed statistical advantage of the Lutonix DCB. It would not have been state of the art at the time that this trial was initiated to use 2.0. There had been data that had emerged in the peer-reviewed literature suggesting that 2.5 or greater was a superior endpoint.

There was another question about the continuous variable. There is a slide that we have that shows that.

DR. DeFORD: PE-58.

DR. JAFF: As we put this up, let me notify the Panel that PSVR has not been validated in the peer-reviewed literature as a continuous variable. It has not been used as a continuous variable in any previous published peripheral artery disease device trial. And in this particular study,

as in the others that were shown earlier in the core presentation, all of the previous IDE trials have used PSVR as a binary measure of restenosis, that is, greater or less than 50%. However, the Sponsor did run this continuous variable analysis of PSVR. A couple of comments to note before I respond to this particular slide.

There were total occlusions in this that would have clearly been hard to adjudicate on this, using this as a PSVR ratio with a number since it was occluded. So we actually took the conservative route and gave that a very high PSVR of 9, and that was put in for all of those occlusions. And these values were obtained excluding anybody who had undergone a TLR. So these are results after the intervention. And what you'll notice is that comparing the standard PTA to the drug-coated balloon, along the vertical axis is the cumulative percentage and on the horizontal axis the PSVR.

Under 2, both groups compared similarly with about a cumulative frequency of about 60%. Above 4, both groups compared similarly with a PSVR up in the range of high 3's to 4. And you'll notice, between 2 and 4, there is a separation showing you an advantage of the drug-coated balloon, with the PSVR at 2.5 showing that comparing the blue line to the red line.

So this was an analysis done specifically to answer this question. But, again, as I mentioned before, this has not been validated in the peer-reviewed literature and is not routinely used in clinical trials.

DR. DeFORD: Thank you, Dr. Jaff.

DR. PAGE: Thank you.

And in terms of our deliberations, we will be discussing these data when we deliberate as a panel. So I'll ask the Panelists only to ask questions if they specifically need clarification of what's been shown.

Dr. Lange.

DR. LANGE: It's not on the slide. I assume that's the PSVR at 12 months.

DR. DeFORD: Yes.

DR. LANGE: Okay.

DR. DeFORD: I'm sorry. Yes, that is. That's 12 months.

DR. LANGE: And then was a similar analysis done on people that had TLR? Before they had their TLR, did they also have it? Could you have excluded those people from this graph?

DR. DeFORD: Certainly we didn't create that graph looking specifically at patients who had had a re-intervention, so I apologize for that.

The next question that I have is -- these really were brought together. Dr. Lange and Dr. Cigarroa had asked about what endpoint -- what drove TLR was one question, and the other question was could we look at data by duplex ultrasound and TLR -- so what drove the primary endpoint? And we break that out. So if we could pull up PE-59, please.

Just to orient you to this, there were 92 DCB and 64 standard

PTA binary restenoses or failures in this study. About one-third patency in both groups was driven by TLR -- 38% in both arms -- and two-thirds were driven by duplex ultrasound. In each case of TLR, though, each of those patients who had failed had a binary restenosis.

So, in this particular study, the rate of primary patency and the binary restenosis rate -- so 1 minus that -- are exactly the same, which is a little unusual. So, in the TLR, here we did see a difference, as we discussed earlier, but there was no difference in re-interventions.

So, again, what this states is that physicians were blinded. This is a very unusual result, in fact, and I could show you data about other studies where you see quite a difference between treatment and control. But due to the blinding, we believe that this drove, very clearly, the same kind of re-intervention rate, based on clinical symptoms, of 38% in both arms.

DR. PAGE: Yes. Dr. Lange.

DR. LANGE: So just for clarification. Every patient that received TLR, it was done because of restenosis, not because of symptoms?

DR. DeFORD: It was done because of symptoms, but in every case they had a restenosis.

DR. LANGE: But it looks like there are two-thirds of the patients that also had restenosis but did not get TLR.

DR. DeFORD: That's correct.

DR. LANGE: Okay.

DR. DeFORD: Maybe I could have Dr. Ansel speak to this, but it's very common that patients with binary restenosis may not require a re-intervention based on symptoms after a procedure.

DR. LANGE: All right, thanks. I'm just trying to figure out why.

DR. PAGE: I think Dr. Lange is clear. I'm not sure we need another comment.

DR. DeFORD: Okay, great. Thank you.

DR. PAGE: Is that okay? Thank you.

DR. DeFORD: That was fine. I just want to make sure we gave you what you needed.

Okay, the next question was also from Dr. Lange. What percent of lesions in the study were de novo versus restenotic? And so if I could have Slide AA-15, please. That's not what I'm looking for. So I'm looking for a slide that's a table with target vessel type, de novo/restenotic. There we go.

Okay, if we look at this, we've provided you both primary patency and safety results based on those patients with de novo lesions and restenosed lesions, and you can see very similar treatment effect between both groups. And then in the restenosed vessel, again you see a difference in safety driven by some re-intervention, apparently, but again generally supportive.

DR. HIRSHFELD: Can I just clarify something? Sorry.

DR. PAGE: Yes, Dr. Hirshfeld.

DR. HIRSHFELD: Sorry. My apologies for butting in.

If I interpret this correctly, the restenosis rate in restenotic lesions was identical to the restenosis rate in de novo lesions.

DR. DeFORD: That's correct.

DR. HIRSHFELD: Okay.

DR. DeFORD: In the Lutonix DCB, 65.2 versus 65.1.

DR. HIRSHFELD: Yes. This is certainly virtually unheard of in the coronary literature, because re-dilating restenotic lesions in the coronary literature is saddled with the much higher intrinsic restenosis rate.

DR. PAGE: And that's just in the Lutonix, in the drug-coated balloon. There is a higher in the standard.

DR. DeFORD: There's actually a higher primary patency in both.

DR. HIRSHFELD: The difference in restenosis rates, if I read this correctly, it's lower but it's the same. Yes.

DR. PAGE: So they're both 65 for those with the drug-coated balloon, de novo and restenotic. But the de novo had, as you would have anticipated from the coronary literature, a lower restenosis rate, 52 versus 56 for the standard PTA.

DR. DeFORD: That's actually primary patency. And I would just caution you --

DR. PAGE: I'm sorry, the other way around. But yeah.

DR. DeFORD: -- that we're talking very small numbers here in

the restenosed group. So I think making broad decisions based on that would probably be very difficult.

DR. PAGE: So actually what you're pointing out, Dr. Hirshfeld, is actually the restenosed stayed open more in the standard PTA and they were equivalent --

DR. DeFORD: Yes, and that's true with only 16 patients.

DR. PAGE: -- in the drug-coated balloon.

Other comments from the Panel?

Dr. Cigarroa.

DR. CIGARROA: As I look at this slide, two comments. And correct me if I'm misinterpreting. So stratified by de novo versus restenosed, efficacy in terms of primary patency and freedom from primary safety event, both demonstrated in the de novo and the restenosed numerically by statistical analyses -- similar but likely underpowered -- and that is, we don't see the same treatment effect but recognizing the sample size is small and this is a post hoc analysis.

DR. DeFORD: That's exactly correct. Yes.

DR. CIGARROA: Okay, I just wanted to --

DR. DeFORD: Yes.

DR. CIGARROA: -- be clear.

DR. DeFORD: Okay, the next question I have was also from --

DR. PAGE: Dr. Posner.

DR. DeFORD: Oh, I'm sorry.

DR. POSNER: I just have a very naive question. How important is that?

DR. PAGE: We will discuss that when we undertake our deliberations.

DR. POSNER: Okay, because when we hear that these things can't really be --

DR. PAGE: You raise a good question. We'll address that when we're speaking among ourselves, so please hold that question.

DR. DeFORD: The next question was also from Dr. Lange, and he specifically had requested information on was the vessel normal on either side of the lesion for the PTA group with geographic miss. And I just want to clarify that this was duplex ultrasound, so we didn't actually have imaging data to show what the vessel looked like on either side of the lesion. However, we do have procedural results that I can share on percent diameter stenosis in both groups. If I could have Slide PE-31. Some of the procedural outcomes.

Again, this is a cumulative distribution that we've pooled together to show you the DCB group on the left, the PTA group on the right. These were patients with geographic miss. And you can see that in both cases the curves on the right are the more stenosed -- so pre-procedure -- and the curves on the left are post-procedure. And you can see that no

geographic miss patients in both arms of the study actually had greater percent diameter stenosis compared to the population that did not have geographic miss. However, at the end of the procedure, the percent diameter stenosis in both groups was the same.

Again, this is a piece of data pointing to the fact that patients may have come in with different lesion characteristics, and it appears that geographic miss actually was an interesting predictor. And we have some additional data we can share on that later on, more CTOs, for example, more calcium. It just was apparent that in some sense, from a procedural perspective, it makes sense that you may not know until you open up that lesion; and then when you go back, if you don't need to touch up, then you end up with a geographic miss in the control arm. But, again, the point is that all of these patients left their procedure with similar results.

DR. LANGE: Thank you.

DR. DeFORD: Dr. Lange asked another question. What percent of women that were evaluated were smokers and which ones were not? If we could have Slide AA-7, please.

This was in the core presentation. We've added the numbers to the right so that you have a sense of each subgroup. The number of patients that were non-smoking males with a patency success -- so 21 over 39 female smokers and non-smokers, again in the U.S. and OUS. So I'll give that a second for you to absorb that if there's additional information. I think this

slide provides the number of subjects that were evaluated in each subgroup. Specifically, the percent evaluated women that were smokers was 28.3%. So that's 41 over 145 patients, so 28.3%. And though data is evenly distributed across the groups, within each subgroup fewer women in the U.S. smoke relative to the OUS women. The p-value for that, by the way, was 0.008.

DR. PAGE: Dr. Lange.

DR. LANGE: Thank you, I appreciate that. If you look at the women who received Lutonix and actually had --

DR. PAGE: Could you leave the slide up, please?

DR. DeFORD: Yes.

DR. LANGE: -- their vessels analyzed, what percent were smokers? And if you look at the women that received PTA and had their vessels analyzed, what percent were smokers?

DR. DeFORD: I'm not sure I understand the question. Every one of these patients had their vessels analyzed by duplex ultrasound or they would not be included in our patency evaluation.

DR. LANGE: Okay. So let me explain it. So there are women who received the treatment balloon. What percentage of those analyzed were cigarette smokers?

DR. DeFORD: Oh, okay, 28.3%.

DR. LANGE: Okay. And the women who received PTA and had their vessels analyzed, what percent were cigarette smokers?

DR. DeFORD: I will have to do that calculation here real quick.

DR. LANGE: Okay.

DR. DeFORD: It's this right here.

DR. PAGE: Maybe we should hold on that graph. So maybe someone in your group could be running those numbers and we can get on to the next question.

DR. DeFORD: We can pull that together.

DR. LANGE: Thanks.

DR. DeFORD: The next question was from Dr. Ohman. What variables drove primary efficacy? And he specifically asked about geography, gender, region, location, and so on. And I'd like to ask Chris Mullin to come and discuss some of the analyses that we did on subgroups and also looking at different variables that affect modifiers.

MR. MULLIN: Chris Mullin.

If I can just get Slide AA-9 for second, we might be able to get that earlier number.

DR. PAGE: And I'll need you to speak up.

MR. MULLIN: Sorry. Chris Mullin.

DR. PAGE: Thank you.

MR. MULLIN: This is just to answer Dr. Lange's earlier question. We do here have, for patients evaluable for primary patency, what the smoking distribution is for the Lutonix DCB group and the standard PTA group

for females. It is broken up by geography, but we can see how geography influences these numbers.

So, for example, on the bottom half you see 23.9% smokers for Lutonix DCB in females evaluable for primary patency versus 22.2% for PTA. But in Europe, much higher prevalence: 40.0% for the Lutonix DCB, 35.3% for standard PTA.

And, in fact, this smoking drives a lot of what we'll talk about here shortly. It's not so much the difference in smoking between the groups, but it's the difference in smoking across the geography/gender subgroups. Smoking being an important variable that influences patency, drives many of the interactions that we saw in the study.

DR. LANGE: Thank you. This is what I asked for. Perfect. Thank you very much.

MR. MULLIN: All right. So to proceed with these additional questions, we have one on the role of gender, geography, lesion location, and smoking. I think it was Dr. Ohman on the phone. If we can pull up Slide AA-11.

So we were able to run a multivariable model looking at both primary patency and primary safety. For reference, on this slide, we've included one row that has an adjusted -- excuse me -- an unadjusted model, so a logistic regression model looking at treatment effect. And then, in the subsequent rows, we've included treatment effect again, but this time

adjusting for the factors of female gender, geography, lesion location, and smoking.

I think there are a couple of points to be made. One is that, for both primary patency and primary safety, treatment effect is relatively consistent with odds ratios nearly identical for the two analyses. And then further, you can see, for primary patency, the significant p-value for smoking in the model, 0.039, again highlighting the role that smoking is important. These individual p-values are a little bit difficult to interpret in the multivariate model, given that smoking isn't a randomized comparison, but it's there nonetheless.

And for safety, in the bottom, you'll see a significant p-value for females when adjusted: 0.019. If we go back to the slides we presented in the core, however, we can see that safety results by gender and geography were driven by results in one PTA group. I can't recall the slide number.

DR. DeFORD: What are you looking for? What information?

MR. MULLIN: Yeah. So it's got the treatment groups, drug-coated balloon and PTA, by gender and geography for safety.

DR. DeFORD: Is this what you're looking for?

MR. MULLIN: It's like this one, except it has it broken down by treatment group, DCB and PTA.

DR. DeFORD: Sorry, just a second here.

MR. MULLIN: Here we go. So the significant difference in

safety for gender is really driven by very low performance in the PTA group in Europe. And the remainder of subgroups, both in the U.S., for males and females, otherwise were generally very supportive of non-inferiority, with very high freedom from safety event rates.

DR. DeFORD: The next question I had was from Dr. Somberg, asking about patient population of comparator studies, so getting more details on comparative studies at 12 months. And so if I could get -- let me look at TD-15 first. Okay, maybe we'll go -- let me look at TD-17 real quickly here. Let me just start back with -- I'm sorry, go back to 15, please. I'm sorry. Let me show you some comparators.

So this is LEVANT 2 and LEVANT 1, RESILIENT, a well-known stent study, and Zilver PTX, also a well-known stent study. With comparative data on age in both groups, you can see that they're quite comparable across all of these studies. Percent of females was also quite similar. Again, many of these variables, it's a little bit --

DR. SOMBERG: The question was on efficacy in terms of patency --

DR. DeFORD: Okay.

DR. SOMBERG: -- and functionality and possibly a six-minute walk or something compared to the stent population versus the DCB.

DR. DeFORD: Let's go back to the slide from earlier today. Yes, here we go. I apologize. We do not have specific other comparators like six-

minute walk and WIQ, for example, or other pieces. What we do have is primary patency and the rate of re-intervention -- so TLR -- across those groups.

DR. PAGE: Dr. Somberg, your light is on. Are you asking a question?

DR. SOMBERG: Oh, sorry.

DR. PAGE: Okay, Dr. Cigarroa.

DR. CIGARROA: Just a point of clarification about definitions of primary patency here. Given that there were different peak velocities, systolic ratios utilized, and Zilver PTX didn't include freedom from target lesion revascularization, can you define primary patency? Are we utilizing the same thresholds and the same definition?

DR. DeFORD: So we are not, in all of these studies. RESILIENT used a 2.5, so the same as LEVANT 2. Zilver PTX used 2.0. I, off the top of my head, don't remember the others. I will say again, just as a reminder, in LEVANT 2, every patient who had a patency failure had a binary restenosis. So the TLR rates, I think there's a difference there that would be important to understand.

DR. CIGARROA: I just wanted to make sure that we, as Panelists, know that primary patency, both in terms of peak systolic ratios utilized and the inclusion of freedom from TLR, was different across these different trials.

DR. DeFORD: That's correct, that's correct.

DR. PAGE: And, Dr. DeFord, you showed us --

DR. DeFORD: Oh, I'm sorry.

DR. PAGE: Just before this slide, you showed another slide just comparing the population, the diabetic, the female and the like.

DR. DeFORD: Yes.

DR. PAGE: And that was in response to another question that was specifically asked. I think Dr. Posner might have asked whether -- or maybe Ms. Chauhan asked the question -- and I don't think you got a chance to reflect on this slide, in terms of the Panel seeing this and being satisfied that the population that we're seeing, at least relative to other populations studied, looks fairly similar.

DR. ZUCKERMAN: I think I asked that question. And I would agree with you, Dr. Page. Other than the fact that, I presume, in the other trials there wasn't allowance for treatment of a popliteal region, in this trial there was. However, there are a limited number of patients in the popliteal region in this trial.

DR. DeFORD: That's correct, Dr. Zuckerman.

DR. PAGE: Thank you.

DR. DeFORD: So I think -- very similar -- there tended to be more Rutherford 4's in our study and one of the other studies, and most of the other studies did not include Rutherford 4's.

We had the question from Dr. Simon on analysis of primary patency without runoff or to remove those patients that were outside the inclusion criteria.

And I do want to remind the Panel, that determination that I showed you this morning was based on core lab adjudication, not the site. The sites did state that they had a runoff vessel.

That said, if we could have PE-117. If I could take a look at that. Yes. I think this answers the question on primary efficacy results by runoff vessels. And then we have another analysis that I'll get to in just a second for you.

But you can see, with similar results, no clear differences observed. There were a number of patients, as you noted, with zero runoff vessels by core lab adjudication, which likely meant that they had 30% or 40% patency versus stenosis. They had 34% or 60% to 70% stenosis. And so the core lab would have adjudicated them as a binary restenosis and zero runoff vessel.

I think there was another analysis you specifically asked for -- was if we excluded the patients with zero runoff vessels, what the results would look like. I think that's Slide AA-8.

So if we look at success rate, primary patency, for one to three runoff vessels or no runoff vessels, you can see, in patency, the results are still significant in both groups, although with no runoff vessels, interestingly,

the Lutonix DCB with a small -- again, you have to be very careful here, very small numbers -- appears to look better. And then, from a safety perspective, although the p-value here -- as you can see, we lose quite a bit of sample -- the results are still quite consistent.

DR. SIMON: (Off microphone.)

DR. PAGE: Please turn on your microphone.

DR. SIMON: Sorry. No, I just feel like -- I hate to put you through the exercise, but this per-protocol group and what the denominator is becomes very important. And so I almost feel we've made this decision to remove the geographic miss -- you know, the analysis was done that way, but there are perfectly valid reasons to remove this group, as well. I'm not sure I agree. We can talk about it in a moment, but I just think the numbers are so close to a margin here of safety and efficacy so that removing patients changes things. So, anyway, it's just good to see.

Thank you.

DR. PAGE: We'll be discussing that as a panel.

DR. DeFORD: That's a very important point. I would just like to remind the Panel that our primary analysis was the ITT population. Certainly, the per-protocol was --

DR. PAGE: We're all familiar with the primary analysis.

DR. DeFORD: Yes.

DR. PAGE: Thank you.

Dr. Lange.

(No audible response.)

DR. DeFORD: Okay.

DR. PAGE: Dr. DeFord, please proceed. You're going great.

DR. DeFORD: Yes, thank you.

Dr. Posner had asked the question on walking distance. When limited, did you verify if this was due to claudication or pulmonary result? Walking distance was self-reported, and we did not collect that information, so I apologize.

We'd also gotten the question from Ms. Chauhan on racial configuration for women in the U.S. and Europe. Could I look at Slide AA-4, please? First, we'll show you some of the demographics. This study had no non-white patients enrolled outside of the U.S., and you can see that, from a race perspective, it's very small numbers of non-whites enrolled within the U.S.

DR. PAGE: Thank you.

DR. DeFORD: Then we had a question from Dr. Somberg. How do stents compare to the results? So I'd like to -- so with or without bailout stenting. If we could look at CO-70. This was from a discussion earlier today. You can see that bailout stent status -- there was favorability for the Lutonix DCB in patients that had a bailout stent.

Again I caution you, very small numbers, only 8 patients in the

treatment arm and 11 in control. A very, very low rate of bailout stenting overall. Only 4% in the study.

Then, if I could just take a quick look at Slide CO-70. I'm sorry, PE-95. Thank you for showing me the same slide, guys. This just breaks it out a little bit more granular for you. Patients with bailout stenting, Lutonix DCB and without, you can see that there was a significant difference there in primary patency.

Then Dr. Cigarroa had asked specifically about medication therapy, the presence or absence of revascularization, and this was specific to cilostazol. So if I could look at Slide PE-72, please.

If we look at our primary patency and freedom from safety events -- first off, I caution, there were very small numbers of patients on cilostazol in both arms of the study. You can see that results are similar in both groups. But, again, I think it's hard to interpret with such small numbers of patients. And safety seemed to be very similar.

Dr. Somberg had specifically requested learning curve for operators. And so if I could look at Slide PE-12. We did analyze efficacy endpoint by the number of procedures, and you can see by site that there was really no difference in efficacy result by number of procedures for the DCB arm. Interestingly, the more experience you had, the PTA arm seemed to not do as well.

DR. SOMBERG: The corollary to the question was, were the

OUS operators more experienced than the U.S. operators?

DR. DeFORD: We didn't specifically try to characterize that. Again, this was really standard PTA. It's a well-known procedure, and clinicians are certainly quite familiar with the PTA procedure. So we didn't look at that specifically. But, again, we would see this by number of procedures here, and we don't seem to see a difference.

We also had a question -- and I'm sorry, we didn't capture which clinician or Panel member had asked this, and it was specifically a question of was it possible to blind the treating physician. And I'd just like to pull up Slide PE-65. We only talked very briefly about this, and I just want to show you pictures of a standard PTA device and a Lutonix drug-coated balloon, the Lutonix drug-coated balloon on top.

We did try to create a device, during the development process, that would look the same. And, in fact, what we tried to do initially was just simply remove the paclitaxel so that you just had the two excipients, sorbitol and polysorbate. Unfortunately it actually didn't look the same, and without introducing other variables that were uncontrolled, we chose to continue to move forward without blinding the physician. We just didn't have a good way to do that.

Dr. Posner had asked about baseline demographic females, U.S. versus OUS, and potential TLR drivers and some procedural details maybe. Let's go to BD-91. Let me just take a look at that. If we look at baseline

characteristics, all females -- so Europe and the U.S. -- there are some differences that you can see. Smoking was certainly a difference between groups. You can see that there were more diabetics in the U.S., more hypertension in the U.S., more previous coronary artery disease and previous history of re-intervention. And that did reach the level of statistical significance.

Our covariate analysis, which someone will talk to in just a couple minutes, I think, describes some of the differences that we found in outcomes, but I don't think any of these were key drivers, although there certainly are differences.

And so the next question was similar -- and I'm not exactly sure of the clinician or Panel member who asked this -- the dataset of covariates and any important differences to explain female differences. So I'd like to ask Chris Mullin again to come to the podium and discuss this a little bit further.

MR. MULLIN: Chris Mullin.

So I'll walk through some of the differences in gender, starting with Slide BD-95. It was BD-95. There it is. I think this has some of the data from earlier, including smoking as a significant difference, diabetes, hypertension, previous CAD. Previous MI has a p-value of 0.086. So there were some small differences between U.S. and OUS females. Again, the largest one that seemed to drive outcomes was smoking.

You can advance to Slide BD-96. And we'll keep going through

a series of slides here. History of coronary revascularization, significantly different.

DR. DeFORD: Ninety-seven?

MR. MULLIN: Ninety-seven. Rutherford grades similar. ABI slightly higher in the U.S. Similar ABI of the contralateral limb.

Ninety-eight I think we're on. No difference in number of lesions treated. Similar target lesion length. The treated length is 0.053, slightly larger in the U.S. Slightly less maximum percent stenosis in the U.S. 0.005 for the p-value. No difference in calcification at the bottom of the slide.

The next slide, BD-99. No difference in total occlusions. A bit higher -- significantly higher number of patient runoff vessels, 2.1 in the U.S. versus 1.8 outside the U.S. The distribution is in the next few rows. Again, multiplicity is here with these multiple tests, so keep that in consideration. No significant difference in lesion location.

BD-100. Significantly more contralateral access in the United States versus Europe: 93% versus 48%. Similar maximum percent diameter stenosis. Post/pre-dilatation similar. On the bottom you see slightly -- you see the significantly higher transit times and significantly higher inflation times per balloon.

And BD-101. There was less maximum pressure, significantly different: 7.2 versus 8.8. Similar results for dissection. Similar results for

maximum diameter stenosis post-study treatment on the bottom row.

And then I think we'll finally go back to AA-11. I showed this slide earlier, but these sort of summarize some of the comparisons we did to examine these in further detail.

DR. DeFORD: Hey, Chris, don't go far. I think the next one is yours, too.

So the next question from Dr. Lange was geographic miss breakdown, does it explain the OUS versus U.S. differences?

MR. MULLIN: Chris Mullin.

The short answer is no. We did quick examination for efficacy, looking at a treatment by geographic miss interaction. That p-value is 0.67. For safety, similar interaction. The p-value was 0.22. When we fit a model that had the interaction of geography and treatment group, then adjusted for geographic miss, that p-value was 0.165 and 0.03 for safety. So, overall, it didn't drive what we were seeing with regards to OUS/U.S. differences.

DR. LANGE: Thank you.

DR. DeFORD: And, Dr. Page, I believe this is the list of questions that we had captured from earlier today.

DR. PAGE: Thank you very much. Stand by. We may have further questions for you.

Did FDA have anything to prepare?

DR. ZUCKERMAN: By agreement, I think we allowed the

Sponsor to do the detailed analyses that you've just seen.

DR. PAGE: Perfect. And you are satisfied with the Sponsor's responses?

DR. ZUCKERMAN: Yes.

DR. PAGE: Perfect.

DR. DeFORD: I apologize. There was one other question that was directed to the FDA that I neglected to give the answer on. And there was a question about the number of patients to tip the geographic miss, and the number of patients is two.

DR. PAGE: Great. Thank you very much.

We now can begin the portion of our meeting where we, as a panel, deliberate among ourselves. I want to open the floor to the experts sitting here at the table to begin deliberation of any issues that you may have with the data you've heard today, either during the Panel presentations or during the question and answer period.

And I'll just ask anybody to lead off in terms of big picture, questions, concerns. And it's perfect that I see Dr. Naftel's hand go up, because we're all wanting you to help us work through the statistics that we've been presented today.

Dr. Naftel.

DR. NAFTEL: Thank you.

So I want to make one point because there are a number of

statisticians in the room, and I reserve the right to be wrong. But could we possibly go back to Slide 62 from FDA? Is it possible to look at that from that presentation? There's a point I want to make. Kaplan-Meier analysis is just the best thing that's happened to time-related events, but it is possible to use it incorrectly or to not get what you think you are getting out of it. And so it's just a quick point, but it affects all of the estimates of patency.

DR. PAGE: Again, for us to have the slides, it was slide which?

DR. NAFTEL: 62.

DR. PAGE: 62. Thank you.

DR. NAFTEL: Okay, here's the point I want to make. Kaplan-Meier is made to look at events where you know when it happened, you know when a death occurs, you know events like that. You do not know when a vessel becomes non-patent. You don't know that. You look at specific times. So here you can see how there are these downturns at 6 months and at 12 months, and it's because that's when you looked, okay, but it actually occurred sometime before this binary event.

So let's say you had two guys. One came in the day before 12 months, and he's called a non-patent. He's in that estimate, let's just say, for the treatment group, 73.5. He's part of that. If his friend came in the day after, literally the day after 12 months, he's on the right side, and he's part of the downturn, but he's not part of that one-year estimate.

So what I'm saying is, actually, we need to do this a little bit

differently. There should be a single point at one year where you collapse all of those one-year follow-ups. The one-year rate is actually the bottom of that curve, closer to 13 months, when your follow-up visits are over. And so you'd have a much lower patency. Instead of 73%, it's more like perhaps 60%. In the control group, interestingly enough, most of those came in before one year, and most of their events got caught.

So I just want to make a point. I want to make a point that the point estimates are incorrect. And I'm saying that to both the Sponsor and to FDA. And it's all about how you interpret the data. If you said the one-year -- if you slid it over to 13 months, you actually would be fine, and that would be the one-year estimate.

Anybody disagree?

DR. HIRSHFELD: Actually, I think that's the one that they reported the event rates in the tables. I think they included all of those, if I'm not mistaken.

DR. PAGE: Yes, Dr. DeFord.

DR. DeFORD: Yes. Our primary analysis was actually a proportions-based analysis which went through the entire window. And so the 65.2% primary patency at one year versus 52.6% in the control arm is the proportions-based through the 13-month window.

DR. NAFTEL: And thank you. So just enjoy the Kaplan-Meiers and don't pull point estimates off of them. It's the only time I've ever said

that in my life.

(Laughter.)

DR. PAGE: Dr. Naftel, let me press you a little bit more here in terms -- since we were just looking at one analysis and then discussing the primary analysis. And in terms of the primary analysis, do you have concerns with the way this was set up prospectively? And what I'm hearing is the nice occasion where both FDA and the Sponsor appear to be in agreement that the primary analysis in terms of safety and in this case effectiveness were met. Do you have a problem with that interpretation from both FDA and the Sponsor?

DR. NAFTEL: I appreciate you asking me. I'm sure we all have opinions. I agree with the agreement between the two groups. I think that's nice. I think the discussion --

DR. PAGE: We agree they agree, but do you agree?

(Laughter.)

DR. NAFTEL: I agree, with the caveat that I'm sure the focus of the discussion is going to be the subgroup analyses between the outside the U.S. and the females.

DR. PAGE: Good, perfect. Thank you.

Dr. Cigarroa.

DR. CIGARROA: So I'd like other Panel members to comment on the significance of the primary patency in the intention-to-treat group,

and that is, when I look at the data now, post-afternoon, with the clarifications, I come away with the fact that with the clinical endpoint of symptoms, there's no difference. I think the statement was made that revascularization was driven by symptoms and was equal in both groups; is that correct?

DR. PAGE: Dr. DeFord, do you want to comment?

DR. CIGARROA: That 38% in both groups under the TLR.

DR. DeFORD: That is the percentage of patients with binary restenosis. In both arms, they got re-intervened upon. So that's not the percentage of patients in both arms total. We're looking at patients who had a binary restenosis. That was a specific measure to point out the lack of bias in the study, where other studies, for example, have shown a difference between treatment and control of between 30% and 66%.

DR. CIGARROA: Thank you for that clarification. I was not sure on that.

The second question that I'd like clarification specifically around --

DR. ZUCKERMAN: Okay. And, Dr. Cigarroa, that's a great point, so I would ask the Panel members to look at FDA Slide 57 so they can see the actual event rates.

And, Ms. Pack, can you help us here, please? Actually, it's not Slide 57, so we won't be able to.

DR. PAGE: That's not the one you want.

DR. ZUCKERMAN: Right. So we'll have to take that slide off, but I think you got the point without the numerical number.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: The second point of clarification. And I'd like comments from specifically those individuals who do these procedures, specifically our vascular surgical colleagues here. A bit of additional clarification of the distinction between the peak systolic velocity of 2 versus 2.5 that has been used in clinical studies. I myself don't know the difference in the sensitivity and specificity between those two values. And one slide that looked at the two showed no difference. And so I want to understand the clinical significance of those two different definitions of binary restenosis.

DR. PAGE: Just for clarification, Dr. Cigarroa -- and we might be able to pull that slide up -- there was no statistically significant difference when it was analyzed in that way. They show the 2, the 2.5, and the 3, and all-comers and statistical significance was evident in every analysis, but the 2.0 being the binary cutoff; is that correct?

DR. ZUCKERMAN: That's correct. For the record, that's FDA Slide 60.

DR. PAGE: So did you have a question about that?

DR. CIGARROA: I wanted to know if anybody on the Panel could give me some additional insights, given that comments from the

Sponsor has indicated that 2.5 was a better value and that was what was agreed upon in the study. But other clinical trials -- and as I went and tried to find the data indicating, in the literature, that 2.5 was a better measure, I couldn't find anything.

DR. PAGE: Dr. Simon or Dr. Gravereaux, do you have a comment about this being -- the 2.5 being the number employed in this study?

DR. SIMON: Actually, what I was going to say is I actually think the person probably in the room best capable of weighing in on this would be Dr. Jaff, if he's still here. I actually don't, you know -- routinely, the noninvasive study is something, sort of, I focus on peripherally and don't actually get into performing, other than knowing that I find, in ultrasound, there's a considerable variability depending on your tech, the lab. And even small angle changes can affect the numbers. But that being said, Dr. Jaff has sort of published extensively in this area, so I would welcome his comments as an expert.

DR. PAGE: Before we call on him, Dr. Gravereaux, do you have a comment?

DR. GRAVEREAUX: I think there will be institutional variability depending upon your relationship with your vascular lab, and I typically would use numerous criteria to determine if there's a need for a re-look angiogram or an intervention in that regards. So we favor more of a higher

ratio at 3 as an alarm bell. But that goes along with potential ABI drop, Rutherford clinical change in symptoms.

DR. PAGE: So if anything, if you were choosing a point, it would be 2.5 or 3 as opposed to going into the 2.0 range?

DR. GRAVEREAUX: For hemodynamic significance, I think, yes.

DR. PAGE: Or for clinical significance?

DR. GRAVEREAUX: Well, that depends on the symptoms. Sometimes we see -- and, again, for numerous variables. We brought up about patient ambulation capacity is multifactorial. So whether there is spinal stenosis or COPD, there's a whole host of reasons why someone will not be as functional. But for a radiographic alarm bell, again, I think we tend to use a 3.

DR. ZUCKERMAN: Yes. And, Dr. Gravereaux, isn't it true that as you go up to 3, you're increasing your specificity? It would be similar to, in the angiography suite, making your cutoff instead of 50%, 70%. I mean, you're just making a higher bar.

DR. GRAVEREAUX: That's what our expectation is, is that we're looking at a 75% lesion at a 3:1 ratio rather than a lower one. But there's variability, as you said, with the techs. There's the oculostenotic reflex looking at an angiogram, which makes it a little challenging sometimes to cross. That's why I think we have a discrepancy sometimes in what the site will report versus core lab, which is why the core lab is critically important.

DR. PAGE: Dr. Lange, did you have a comment? It's okay if you didn't.

(Laughter.)

DR. PAGE: Okay. Dr. Posner, did you have a comment?

DR. POSNER: Yes. Some of the things we've been discussing -- I think what was obvious is that the lesion does get smaller. The vessel opens up and there's better flow. The thing that we're getting hung up on are all of the small things like female versus male, overseas versus U.S. And whenever we look at it -- I'll bow to the statisticians -- there aren't enough numbers to tell us whether it means anything.

DR. PAGE: I think you're cutting to the heart of the matter there. We are going to be addressing this, and when we get to the questions, that specifically is going to be addressed by the Panel.

DR. POSNER: But just to go further on this, I think again, the point will be, does this work up front and does it just need a five-year follow-up to find out, when you get larger numbers, whether everybody should get this or maybe U.S. women shouldn't get it? And that's something we can't solve today -- I don't think we can't solve today.

DR. PAGE: Fair enough. Did the Sponsor want to respond?

DR. DeFORD: I just wanted to clarify that one of the unique aspects of the study was that, at every follow-up point through a year, the clinician who did the evaluation of the patient did not see the duplex

ultrasound until they made the decision on re-intervention based on clinical symptoms. So, in this case, these patients, the clinician would not have known the duplex ultrasound -- so that oculostenotic reflex -- the whole idea was to try to remove that in the study.

DR. PAGE: Yes, Dr. Lange.

DR. LANGE: I'm confused, so I just want to clarify this, John, because I'm looking at a table that shows a Rutherford classification at 6, 12, and 24 months, and there's no difference in class 0 and 1 between the two treatment groups. That's your slide, Table 4.49.

And then there are a number of other qualitative measures. The only one that fell out was the self-reported -- of all the measures, one pulled out. But what you're telling us now is that people got target lesion revascularization on the basis of symptoms without the physician seeing the ultrasound results.

DR. DeFORD: Let me just clarify. So the clinician made the decision on the re-intervention before looking at the duplex ultrasound result. That was the intent of the study and that's the way the study was conducted. Obviously, once they had determined, based on clinical symptoms, that the patient needed a re-intervention, they of course looked at all of the available information. And if we could go back to -- we have a slide of all the different subgroups, and it's a forest plot.

DR. LANGE: Can you pull up Table 4.49?

DR. DeFORD: I'm sorry.

DR. PAGE: The Sponsor is pulling up the slide now.

DR. DeFORD: I was trying to show all of the different secondaries that were evaluated in the study, and you can see that everything trended in benefit of the drug-coated balloon, virtually, with the exception of ABI, which is right about even across the two groups.

And so although we didn't power it for any of this, and we also had these very unique study design aspects that made it difficult for us to even know what the power calculation should be for any of these secondaries, the preponderance of evidence here is that if there were -- if the DCB was not effective or was not doing something positive, then you would expect to see much more broad variation here versus the positive trending. Again, it's not statistically significant, as you pointed to before.

And then I do have that table for you that I can just pull up here. And this is the table that you were specifically referring to?

DR. LANGE: Right. So, for example, at 12 months, Rutherford classification 1 and 2 for the test DCB A group, it looks like it's 75.7, and in the control PTA C group it looks like it's the same thing. It looks like it's 70.9.

DR. DeFORD: I'm sorry, I'm --

DR. LANGE: Just the class 0 and 1 -- 0, 12 -- excuse me -- 6, 12, and 24 months, they look similar --

DR. DeFORD: Sure.

DR. LANGE: -- as class 0 and 1.

DR. DeFORD: Okay. So if I'm looking at class 0 at 12 months, the DCB group, 51.7% of patients versus 42.7% of patients in PTA.

DR. LANGE: That's asymptomatic or mild asymptomatic. So when you add the two -- because you wouldn't do a procedure on somebody that's mild asymptomatic.

DR. DeFORD: No, that's correct. Yes.

DR. LANGE: Okay.

DR. DeFORD: Yes. I'm sorry, this is specifically showing the Rutherford class. It's not showing re-intervention.

DR. LANGE: Right. I'm just trying to clarify, because I thought the point you were making is that they got TLR because they were symptomatic. But it looks like the people that are asymptomatic or mild asymptomatic are the same for the DCB group and the PTA group. In other words, there wouldn't have been a reason to do a TLR if they're asymptomatic.

DR. DeFORD: That's correct.

DR. LANGE: Okay, thank you.

DR. PAGE: Ms. Chauhan, Mr. Thuramalla, or Dr. Posner, do any of you have any questions during this deliberation period, where we're specifically speaking among ourselves and asking the Sponsor if they have any answers to our questions?

MS. CHAUHAN: I'm just very interested in getting to the issue about the U.S. women.

DR. PAGE: I promise, we will get there.

MS. CHAUHAN: Okay.

(Laughter.)

DR. PAGE: Mr. Thuramalla.

MR. THURAMALLA: This is Naveen Thuramalla.

Not at this time. No, I don't have any questions at this time.

DR. PAGE: Great. Thank you.

Dr. Posner.

(No audible response.)

DR. PAGE: Okay. Are there any more questions that we might be asking of the Sponsor? Or the next step will be to go into our own deliberations as well as addressing a number of issues. We have a lot of questions today, but the nice thing is they're addressing a number of the issues, and I think it will be helpful for us to focus our discussion as we go through the questions.

So at this point I'm looking around and wondering whether this might be an appropriate time to take a break and then after that we go into our discussions. I'm hearing from Ms. Waterhouse that she wants further -- or that we have the option of having further discussions, which we've just been doing, before the questions.

DR. LANGE: May I ask the Sponsor just one question, please? Again, just to put it in the record.

Obviously, the patients here know which treatment they got, but it's a blinded study. And my assumption -- but I just wanted to put it in the record -- is that they were notified after the study was completed, as to what their treatment was, and that is, during follow-up, they were unaware of things.

DR. DeFORD: Yes, that's exactly correct. Patients and follow-up physicians were blinded through 12 months.

DR. LANGE: Great.

DR. DeFORD: After 12 months, they were unblinded.

And then, since I've got the opportunity, I wanted to clarify that when we looked at that chart on Rutherford class, those were the raw numbers at 12 months. So patients who had a re-intervention in the control arm in that 12-month time period would have had an improved Rutherford class and would have been listed there.

DR. LANGE: Thanks, I appreciate the clarification. Thank you.

DR. PAGE: Dr. Zuckerman, give us guidance in terms of our closed deliberations. We've undertaken deliberations here. My impression is, given the number of questions we have, that our closed deliberations are really going to be best worked around the questions you've provided us. Or do you care for us to have more open --

DR. ZUCKERMAN: No, I would agree. I think they will structure the analysis along extremely key lines and will provide the FDA with maximal information.

DR. PAGE: So then with that, I think we will take a 15-minute break, and we'll reconvene at 10 minutes of 3:00.

(Off the record.)

(On the record.)

DR. PAGE: Right now, just to remind the Panel, we're in the part of the meeting where we're deliberating among ourselves. If we need to open the floor to others, we'll only do so at our request. We're going to be discussing what we've seen and heard and read regarding this PMA. I am going to lead us into the questions because I want to make sure our discussion is structured around all of the very well-identified issues around this.

Before we get started, though, FDA has put together a slide that I think addresses one of the questions that has been raised, and that is how endpoints were met. And Ms. Pack is going to show a slide that's been put together that I think will help us understand the outcome results.

Ms. Pack.

DR. BUCKLEY: Hi. This is Donna Buckley.

Just to sort of add to our prior presentation --

DR. PAGE: Dr. Buckley.

DR. BUCKLEY: That's okay.

We had originally broken down, in our presentation, what proportion of the primary patency failures were related to TLR versus binary restenosis where a little over a third were secondary to TLR and the remainder were secondary to binary restenosis. But we failed to provide information in terms of the overall cohort what the failure rates were related to TLR and binary restenosis in each group. So this is the slide we were asked to prepare over the break to sort of break that down to show what the differences are between groups.

DR. PAGE: Are there comments from the Panel?

Dr. Cigarroa, I think you had some question about what was driving endpoints, you and Dr. Lange. And we've seen that a third were TLR and two-thirds were adjudicated restenosis, and this is breaking down the numbers.

Any comments or questions?

Dr. Simon.

DR. SIMON: Do you have a p-value of these?

DR. ZUCKERMAN: No. We're not professional statisticians, but I think the point is that the trends are in the expected directions. These are subgroups again, and we just did the best we could to try to show you that for each component of the endpoint, the trend would be in the expected direction.

DR. PAGE: And the p-value for the primary endpoint for effectiveness was statistically significant, as you know.

Dr. Hirshfeld.

DR. HIRSHFELD: Yes, I just have one question about these data. The control primary patency failures seem to add up to more primary patency failures than -- in this analysis than was in the regular analysis. The test, the DCB failures, seem to be about the same, but it seems like you've got --

DR. ZUCKERMAN: Dr. Hirshfeld, I would refer you to FDA Slide 50, which -- please do not put up on the screen, Lindsay. But 1 - 53% is the control right there.

DR. HIRSHFELD: We've got 40 and 17.8, which is --

DR. ZUCKERMAN: Okay. That is probably the cell 4 should be 30%. Donna, did you do the math wrong?

DR. BUCKLEY: It's possible that we did quick math incorrectly. We can double-check that for you.

DR. PAGE: Other comments or questions from the Panel?

Dr. Lange.

DR. LANGE: Go back again. I just want to, again -- and then she's getting that slide, correct, so we can take a look at it? Can we go back to that?

The adjudicated restenosis without TLR in the test DCB group, if there are 35 patients that had TLR already of 264, that denominator couldn't

be any higher than 229.

DR. ZUCKERMAN: Okay, I don't think the numerator/denominators are correct. But, Donna, did you take one-third of the actual event rate and two-thirds?

DR. BUCKLEY: No, we did a quick calculation based on the denominators in the ITT group overall for primary patency and then took the individual failures based on TLR and restenosis and took that ratio. We're certainly open to the Sponsor's view of this data, as well.

MS. PACK: Would you like me to pull up where we pulled the numbers from? Do we have something better?

DR. DeFORD: Could we have --

DR. PAGE: Dr. DeFord.

DR. DeFORD: -- Slide P-60, please?

I'm sorry. Dr. John DeFord.

DR. PAGE: Go ahead. Did you have a comment?

DR. DeFORD: I was just going to show a slide.

So maybe this breaks it out a little bit more. Detail of 92 patients of 264 and primary patency failure in the DCB versus 64 of 135. And then I think these numbers are very similar, but the denominators here, you see, are the same.

DR. PAGE: So, to summarize, they're going in the same direction.

DR. DeFORD: Yes.

DR. PAGE: Both sets of data appear to be necessary for the primary endpoint.

DR. DeFORD: Yes.

DR. PAGE: But this is largely driven by the DUS.

DR. DeFORD: That's correct.

DR. PAGE: And, again, just to remind the Panel, the primary endpoint was the predetermined combination of these two. So it's a composite endpoint.

Ms. Pack, did you have anything else you were going to show us?

MS. PACK: No, thank you.

DR. PAGE: Great, thank you.

So, at this time, I'd like to focus our discussion on the FDA questions. Copies of these questions are in your folders. I want to remind the Panel that this deliberation period is among Panel members only, and our task at hand is to answer the FDA questions and to discuss them frankly based on the data in the Panel Packs, the presentations we heard this morning, and the expertise around the table.

With this said, I'd like each Panel member to identify him or herself each time he or she speaks unless you've been called upon, which is what I would prefer, and then that will be in the record already and that will

facilitate transcription.

So we have the questions here, and there is a significant preamble for the indications for use. I will be asking Ms. Pack to read these questions as they are projected, and then we will take them one at a time. And this will help direct our conversation.

Ms. Pack.

MS. PACK: I'm trying to project. I don't know if the AV group needs to switch it. It's not letting me.

DR. PAGE: We're looking for the slides to be projected.

MS. PACK: Great.

DR. PAGE: There we go.

MS. PACK: Would you prefer that I read both parts -- or all parts of the questions or stop after each part?

DR. PAGE: Let's take them one part at a time.

MS. PACK: Great. So Question 1, regarding the indications for use, Part (a): As no data were presented involving the use of the Lutonix Drug Coated Balloon without pre-dilatation, please comment on the need for pre-dilatation to be discussed in the indications and/or labeling.

DR. PAGE: Now, early on the Panel heard my comment about this question and Dr. DeFord's response. I'm interested in the Panelists' perspective on this labeling.

Dr. Cigarroa.

DR. CIGARROA: Thank you.

So under the indications for use it states that the Lutonix Drug Coated PTA Catheter is indicated for improving luminal diameter for treatment of obstructive treatment of obstructive de novo or non-stented restenotic lesions, da, da, da. Interestingly, in the way the study was designed, this particular balloon is being used as an adjunctive tool on top of PTA in order to attain a long-term benefit assessed at 12 months. The way the IFU is written is a bit confusing to me, given the way the study was designed. And so I actually think that it is an adjunctive component of a procedure to result in a long-term benefit. Not the acute procedural --

DR. PAGE: So given that point, would your indications specifically state that this would be performed after pre-dilatation?

DR. CIGARROA: As a study design, yes, although there is data in specifically the THUNDER trial that indicate similar drugs/slightly different balloon that shows efficacy.

DR. ZUCKERMAN: Okay, those are excellent points, Dr. Cigarroa, but for the other Panelists, FDA is looking in a label, generally, to truthfully represent what was studied in the FDA trial, and that's why you've gotten us off to the right start. And if we could hear from you and other Panelists along that line.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: So based on the data presented, I believe it is

an adjunctive device in order to attain an improvement in long-term outcomes. So, therefore, yes to pre-dilatation.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I'm glad you got to that point. Yes, I think it's critical -- we're not here to evaluate another balloon in another study that was in Europe. That's irrelevant data, really. So I think we have to focus in on what was presented here, and I think pre-dilatation is important. And I think, also, we have to -- and I don't know if the Chairman wants to talk about it now or later, because we have to talk about the gender and the other big elephant in the room, which is stents.

DR. PAGE: We will get there.

Dr. Posner.

DR. POSNER: Just to confirm what my colleague said. I think it's important to say it's adjunctive and it's explaining why you do need the pre-dilatation. Not just say pre-dilatation. I think adjunctive is important because that's been pointed out. Because we don't know whether -- all the good things really due to the drug being delivered to the wall of the vessel, whether the pre-dilation adds to the ability of the drug to do its work. So I think adjunctive is really important to be included.

DR. PAGE: Well, just to be clear, there was the pre-dilatation followed by standard balloon use in the PTA group.

DR. POSNER: Right.

DR. PAGE: So that procedure was performed in both groups, pre-dilatation and then the second procedure.

DR. POSNER: Right. And so there is something that's adjunctive and it's additive, but you don't have something that just shows the balloon by itself. And that's why I say I think it's important to say it's an adjunct.

DR. PAGE: Great, thank you.

Dr. Gravereaux.

DR. GRAVEREAUX: In the same vein as the semantics of the trial, though, there was an inclusion or a decision point to be made based upon the success of the pre-PTA, and if it was unsuccessful, then it fell off to stenting or bailout. So by design -- and we brought this up earlier -- it was a pre-PTA to a lesser degree of diameter than the nominal vessel, which you ultimately wanted, so it's still a mechanical dilation. It's not just drug delivery. There's still baro pressure exceeding the pre-dilatation, but to separate that out, I think, is there a need for -- that's the question.

Is there a need, then, to say -- well, stipulate if the pre-dilatory balloon effort doesn't work based upon dissection or loss or inadequate luminal gain, is this not indicated anymore? Or do you need a mechanical --

DR. PAGE: Well, I don't know that we would need to provide a contraindication, but certainly the indication, you're suggesting, not only be after pre-dilatation but it be after successful pre-dilatation as defined in this

trial?

DR. GRAVEREAUX: That's the semantics of the trial. And if you have a lesion which has complete recoil with zero luminal gain on your pre-dilatation, it's hard to expect that somebody who does this day in and day out, that another balloon inflation with drug on it is going to make that much of a difference. So the real-world use of this is going to be probably after stenting as much as it will be just as a standalone PTA.

DR. PAGE: I'm looking at head nods in agreement.

So, Dr. Zuckerman, if I may -- and Panel, please contradict me if I'm not accurately reflecting our discussion -- but if I may, with regard to Question 1a, the Panel is recommending that pre-dilatation and even perhaps successful pre-dilatation, as defined by this trial, be written into the indications for the use of this device. Is that adequate for 1a?

DR. ZUCKERMAN: Yes, that's very helpful. And I would note, also, that the Sponsor indicated that they were acceptable with that.

DR. PAGE: Great, thank you.

Ms. Pack, would you please read Question 1b?

MS. PACK: Yes. Please comment on any other aspect of the proposed indication for use, and discuss any revisions to the indications that you would recommend based on the information in the Panel Pack or as discussed today.

DR. PAGE: I've already heard the comment that it shouldn't

just be pre-dilatation, but effective pre-dilatation. So we've already addressed that. Are there any other aspects of the proposed indication?

Dr. Cigarroa.

DR. CIGARROA: So, again, the semantics with regards to improving luminal diameter, what we see are at follow-up the surrogate of restenosis being peak systolic velocity ratios. And so I'm not sure that I would indicate for improving luminal diameter acutely. I don't see that dataset.

DR. PAGE: How would you better reflect the results of this study in terms of the efficacy if you were going to argue that there was efficacy?

DR. CIGARROA: So say for improving the long-term clinical outcomes for the treatment of obstructive de novo or non-stented restenotic lesions.

DR. PAGE: Other comments from the Panel?

Dr. Hirshfeld.

DR. HIRSHFELD: Yes. I would agree with what Dr. Cigarroa said. I think the indication, as currently written, could apply to a conventional balloon.

DR. PAGE: Would you say the last part?

DR. HIRSHFELD: The indication, as currently written, could apply to a conventional balloon. That's what they are for. And so I think the indication needs to state something about what the rationale behind this

balloon design is.

DR. PAGE: Thank you.

Dr. Simon.

DR. SIMON: Yeah, why not just say patency? I mean, our endpoints were patency and safety, so why not just say -- come out and say it, for improving patency and safety in the treatment. You know, da-da-da.

DR. PAGE: Other comments?

Dr. Lange.

DR. LANGE: I'm not convinced that we have enough data for restenosis. There were a total of 59 patients who underwent the procedure for the treatment of non-stenotic or for non-stented restenotic lesions, and it was really under-powered to draw any conclusions about whether it would be beneficial or not.

DR. PAGE: How would you describe -- I've heard it said that one description might be long-term clinical outcomes. Would that adequately describe the benefit that might be achieved?

DR. LANGE: I guess I'm more interested in saying for treatment of obstructive de novo lesions and eliminating restenotic because we just don't have enough data about that.

DR. PAGE: So you're unconvinced, when you pull out restenotic or restenotic lesions, that you can't support an indication for that?

DR. LANGE: Of the 399 lesions that were under procedure

performed, 59 were restenosis lesions. And so there's not enough data to know whether this particular procedure is useful in those particular lesions.

DR. PAGE: I guess the question is, if we carve out different groups, we will find a lack of statistical significance in many different subgroups. I'm interested in the Panel as to whether you are inclined to modify the indications for this device based on the fact that even though it met the primary safety and efficacy endpoint for the group that included both, when you carve out one, making the smaller group, you don't have statistical significance when you fail to include that in the indications. I know what your perspective is. I'm interested in other Panelists as to whether they would agree with that.

Dr. Somberg.

DR. SOMBERG: It's frightening, but I agree completely with you, Dr. Page. I really think --

DR. PAGE: I didn't say anything. I'm just asking a question.

(Laughter.)

DR. PAGE: I want to hear your opinion.

DR. SOMBERG: I infer from your statement, I mean, whatever it might be. I think the indication, as stated in Question 1, that the drug coated balloon catheter is indicated for improving -- and for the total, and not to subdivide it or make any qualifications except as it was required in the protocol to have a pre-dilatation.

And I don't think we have to get into whether it was complete dilatation or a little under-inflation because obviously the people who are going to use this are going to have to know those details to make use of this balloon, just like they have to know the details of the inflation pressure of it, et cetera.

DR. PAGE: Now we're getting somewhere. We have two people who disagree. That's valuable. I need other people to weigh in as to your perspective so we can give some guidance to the FDA.

DR. SLOTWINER: David Slotwiner.

I agree. I think that this is not the place to subdivide and be more specific than the original enrollment criteria for the trial. And so I would agree with Dr. Somberg that this should be left as is.

DR. PAGE: While you're at it, Dr. Slotwiner, would you like to weigh in on how you would describe what we're trying to achieve here in terms of the outcome?

DR. SLOTWINER: Well, let me get back to you on that one.

DR. PAGE: Fair enough.

Dr. Cigarroa, did you have your hand raised? No, you didn't.

Dr. Posner.

DR. POSNER: Yes, me again.

And I agree with what was said before, and I would like to make the point on all the other ones that we look at; we're going to have follow-up

data, and hopefully, the follow-up data will get sufficient numbers in the subgroups so you can be more specific one year or two years or three years down the road as to whether this really does work for restenotic lesions versus de novo lesions. But, otherwise, the description at this point, I would say look at the whole group and describe it as prolonging patency.

DR. PAGE: Fair enough.

As I look around to the Panelists, I'm interested whether there are other people who want to carve out the restenotic or would have the indications more describing the indications for inclusion in this study.

Anybody else wanting to join Dr. Lange?

Dr. Hirshfeld.

DR. HIRSHFELD: Well, I think this device is a conventional balloon that has a drug coating. The program that developed it was intended to develop a device that had a beneficial effect on restenosis compared to conventional balloons. And so we're going to decide later on, when we debate the efficacy data, whether we decide that that's been demonstrated or not. That seems to me that the purpose of this device is to prevent or at least decrease the likelihood of restenosis. And if the device is going to be in the marketplace, it should be in the marketplace with that claim and with that indication in its indication data.

DR. PAGE: Thank you. But in terms of those included for use with this, that also included de novo and restenotic lesions. Are you

comfortable including both of those as they were included in the study?

DR. HIRSHFELD: Yes.

DR. PAGE: Okay.

So, Dr. Zuckerman, if I may, this has been a valuable discussion from the Panel. There is, I would say, a majority but not unanimity that the indications would reflect the indications for inclusion in the study. We already mentioned the fact that the device was indicated for patients who clearly have stenosis in the first place. And in terms of the subdividing, help me out in terms of where we are on that. We're not inclined to subdividing those included, but in terms of endpoints, I'm actually hearing a fair variety of perspectives as to restenosis, clinical outcomes.

Perhaps that will take further negotiation with FDA and the Sponsor, unless anybody can better summarize what the committee's perspective is on that. I personally would favor a description of what the endpoints were of the study, which is target vessel revascularization and increased stenosis.

Does that meet your needs?

DR. ZUCKERMAN: Yes, it does. And I think the comments made by Dr. Somberg and you during the discussion were very helpful for framing the rest of the questions in that the Panel will be asked, with most of them, to decide whether the primary treatment effect observed or the so-called average treatment effect is the best estimate of what we're seeing as

opposed to the multiple subgroups we've looked at today for a variety of reasons.

Thank you.

DR. PAGE: Right. And we'll get to those as we continue on.

Dr. Gravereaux.

DR. GRAVEREAUX: I think, not to get bogged down in this, but I think, to your point, this is a balloon, which is an established treatment, with a medication on top, and so from the balloon aspect, the mechanical dilation, it's been well established to use it in a de novo or restenotic and then -- I mean, the great hope is that this will be a magic bullet for in-stent restenosis and all the other things that we, as interventionalists, have to face with these challenging vascular --

DR. ZUCKERMAN: You know, Dr. Gravereaux, thank you for those excellent comments, and I've heard similar comments from other Panel members. It's really important, during this phase of the discussion, to concentrate on what was studied in the clinical trial, to think about an appropriate label and risk/benefit analysis. And this is a huge task for this Panel, and I appreciate everyone's efforts.

I'd really like to ask the Panel not to get bogged down in possible off-label uses. We're certainly committed with the Sponsor to do future IDE trials, but we have to look at a very difficult dataset right now before us.

DR. PAGE: Thank you.

The next question is regarding labeling. Draft labeling was provided by the Sponsor in Section 7 of the Panel Pack.

Ms. Pack, I'll read this for us since I'm already at it.

Please comment on the proposed contraindications, warnings, and precautions in the labeling.

Are there any concerns, comments, about the labeling?

(No response.)

DR. PAGE: I made note of one table where there was comparison of the number of balloons used. Help me if anybody else saw that. And it looked like it did not include the fact that -- it looked like the number of balloons used was measured after the pre-dilatation was achieved. Anybody have concerns about that, or should it be more clear that there may be another balloon used if one uses this device?

Dr. Cigarroa.

DR. CIGARROA: I don't have concerns in that it's a single use, I mean, by design, and therefore if you need to do any additional work, you have to use another balloon. I would not explicitly state that.

DR. PAGE: Any other concerns regarding the proposed contraindications, warnings, and precautions in the labeling?

Yes, Dr. Posner.

DR. POSNER: Yeah, a pharmacokinetics question.

If you use a second balloon, will there be a higher level of the drug added to a point where it becomes a problem? I don't know.

DR. SIMON: I thought that was addressed. You did have more balloons used in the test group, and then they provided an analysis of the dosage of paclitaxel, and it showed not to be an issue.

DR. POSNER: Okay, because when they gave my answer to my question, it was done in animals, so I didn't know whether they wanted to extrapolate the dosage to what might be dangerous in people.

DR. ZUCKERMAN: Your general point is well taken, Dr. Posner. We'll have to review with the Sponsor in detail what, if any, appropriate labeling would be for use of two balloons at the same time. I think, generally, because of the unknown clinical human information, we would warn against it.

DR. PAGE: Dr. Somberg.

Dr. Simon, your light is on.

DR. SOMBERG: I mean, you're going to increase. The more you administer it, you will have a peak level. From one balloon, you will augment that. That's not really been studied in animals. There was no data in the animals and there's no data, that I saw, in people. But at the same time, you have to look to the patients. And, I mean, if you have someone who has real problems and you need to have -- the balloon has a certain length, if it doesn't meet the geographic area, et cetera, you may have to do that. So this

is all within the clinician's decision-making process and I would leave it at that.

DR. PAGE: Fair enough.

So, Dr. Zuckerman, with regard to Question 2, the Panel generally has expressed no great concerns with the indications and contraindications and warnings, as you've developed them. But, clearly, there's going to be more work to do with the Sponsor in terms of the particulars.

DR. ZUCKERMAN: That is great. And in preparation for Question 3, I would ask all Panelists to turn to that page so that they can specifically look at the table that corresponds to Ms. Pack's two questions.

DR. PAGE: Right. And now that gets us to Question 3. And before I ask Ms. Pack to read those questions, I would just emphasize:

The primary safety endpoint is defined as a composite of freedom from all-cause perioperative (< 30 day) death and freedom at 1 year from the following: index limb amputation (above or below the ankle), index limb re-intervention, and index limb-related death.

We've had various discussions about the issues regarding the intention-to-treat and the per-protocol groups.

And, Ms. Pack, why don't you go ahead and read first Question 3a? And, Panelists, please address this table that you're looking at on page 2 of 9 of the question pack.

Ms. Pack.

MS. PACK: Question 3a: Please comment on the robustness of the primary safety endpoint conclusion, given the difference in results depending on the study population used.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: I mean, it's a non sequitur. The results are not robust. We've heard that changing two patients can make a big difference, and we have to face that reality. I think you put it in the context of there's not much additional therapy in the popliteal area where stents are discouraged and the balloon dilatation has a restenosis rate that's high and that there is a strong trend and a good safety profile, so I'm willing to excuse this. But robust is robust and non-robust is non-robust. It's clear.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: So just a little bit of a different view. Intent-to-treat is such a nice concept, and usually the issue is that everybody doesn't get treated as planned. In this case, everybody did. The per-protocol is more about exclusions, whatever. And it seems to me that the per-protocol, the main thing that's happened is the effect size has gone down a little bit, but mainly we've lost some patients.

To me, a p-value of 0.08 -- you know, 0.05 is just a mythical thing made up by a medical editor. 0.05 means nothing. 0.08 -- you know,

look at the p-value, think about it, are you happy with it, that's fine. But I never use a 0.05. So I personally have no concerns at all about the difference in the two analyses.

DR. ZUCKERMAN: Yes. So Dr. Naftel is seeing the glass half full. Where I'd like the Panelists to also comment is was the per-protocol definition, in retrospect, a useful clinical definition that we should use to look at robustness of the data? You've heard the Sponsor make some comments, and how helpful is that per-protocol result, from a clinical perspective?

DR. PAGE: Dr. Lange and then Dr. Simon.

DR. LANGE: In general, I'd say it matches the FDA -- I think it is useful because if you have an excessive number of protocol violations, it can skew your intention-to-treat analysis. In this particular case, the skew was due to a geographic mismatch, which probably doesn't mean very much in the PTA group. So the analysis, yes. And then an explanation, in this particular case, an excellent explanation from the Sponsor, doesn't impact it. But I do think it's helpful to have that information.

DR. PAGE: Dr. Simon.

DR. SIMON: Yes, I tend to second that. I don't know if you could apply the lesson here to every study and say it should be discarded. I actually found it sent us in a wrong direction, I think. I think excluding that group for geographic miss added nothing and, in fact, it was the core lab that picked up the geographic miss. The operators that represented real-world

operators, they themselves reported three patients in total that I think had geographic miss. So I think it actually moved us away from understanding how this tool would have been used in a real-world setting.

Along the same lines of the per-protocol analysis here, there were lesions that were greater than 15 cm that got treated. We didn't exclude those. I don't remember how many there were. There were referenced vessel diameters less than 4 mm. We didn't exclude those. Again, to my point, we violated the inclusion criteria by putting patients in who had no runoff vessels. We didn't exclude those.

So I think, to the credit of the study coordinators and those that were in the trenches, they really stuck to the protocol as best they could, and so I thought the ITT, to a certain extent, represented the treatment group, and it was when you define ITT not as the 316 in the treatment arm, but taking out -- you know, ultimately we got down to an ITT of just in the effectiveness, let's say, of 264 patients. And I thought looking at it that way was probably the correct way. But I thought the PP group here in some way sent us off in a wrong direction.

DR. PAGE: Great.

So I'm looking around, and I think there's agreement that the per-protocol was affected negatively by this geographic miss, and I don't think anybody's really convinced that that is of importance. There is one other feature of the dataset that's being asked about here, and Dr. Somberg

addressed it, and that is the robustness of the trial.

And I'll put it out there as to we see a positive endpoint in terms of safety and efficacy. Trials are designed to be the right size. No one wants to make this trial twice as big as it needs to be. On the other hand, it seems like any time we carve out a population, we seem to lose statistical significance. Is the Panel troubled by that? Is this trial right sized or is it non-robust such that you're not only saying it's non-robust but you're concerned about how you interpret the data?

I'm looking for people's input on that feature of the trial.

Dr. Hirshfeld.

DR. HIRSHFELD: I don't think we can blame the trial design. The trial design was made on the best estimate of what the effect size would be. It appears to me -- and, thus, I think the group needs to discuss this when we get to the appropriate question, but the effect size is small. And because the effect size is small, that's why we're dealing with loss of statistical significance when we lose small portions of the population.

So the issue there is, is it appropriate to design a trial that is so large that it has tremendous statistical power and can detect a very small difference?

DR. PAGE: And let me just ask what you mean by small effect size? Are you commenting on the fact that there's about a 12% difference in the endpoint, or are you commenting on the fact that it barely met statistical

significance no matter what the difference was between the two groups?

DR. HIRSHFELD: Well, the magnitude of the effect size with a primary endpoint, which is modest and appears to be progressively lost in later follow-up, although the number of patients in the later than 12-month follow-up is small. The absence of clinical endpoints, symptomatic endpoints, to demonstrate clinical efficacy in terms of those outcomes, in terms of all the Walking Impairment Questionnaires and the ankle-brachial indices and so forth, which basically show no difference. So I think, when I look at the scenario, all the differences are in the right direction, but they're all very small.

DR. PAGE: Thank you.

Other comments before I try to summarize what I think I'm hearing from the Panel?

(No response.)

DR. PAGE: So, Dr. Zuckerman, with regard to Question 3a, the per-protocol analysis, while it's a valuable analysis in many cases, in this case throws us on the wrong track and takes out a number of individuals who were removed due to technical issues related to the fact that there is an unblinded operator, perhaps. But for whatever reason, we're not troubled by inclusion of those patients that were actually taken out by the per-protocol, and as such, the intention-to-treat appears to be the right population.

In terms of the robustness of the results overall, I'm hearing a

modest clinical effect and a robustness such that the number of patients enrolled in the study was spot on in terms of designing the trial, perhaps, in that it allowed reaching statistical significance. But when the population is reduced in any significant way, we're seeing that the statistical significance, or I should say the p-value of less than 0.05, which Dr. Naftel has now done away with in my mind, but the p-value is no longer met, given the smaller population.

Is that helpful to you?

DR. ZUCKERMAN: That's a great summary of a great discussion by the Panel on this question.

DR. PAGE: Great.

So now let's address the issue of rare adverse events. And it's summarized on page 3, but I will ask Ms. Pack to read aloud Question 3b.

MS. PACK: Question 3b: Based on the sample size needed to detect rare adverse events, the data are incomplete and not powered to detect potential rare adverse safety events. Please comment on this issue.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: So, once again, we just have to apply reason. Data are incomplete. That's not a yes or no. Either it's complete or it's not; they're degrees. And in this case, 561 out of the minimum sample size 869, that's a pretty good chunk, and I believe there were no events. So, really, to

me, that's certainly we'll keep looking, certainly we don't let the post-approval study affect what we do right now, we understand that. But I just have no issues, whatsoever, with the sample size that's been shown at this point.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I must take a different tact. I think the data set for rare adverse events is incomplete, but the 800-and-something that it was set at is also incomplete because -- I come from the drug side of things, and rare adverse events is 1 in 1,000, 1 in 5,000 or something like that, which you probably should expect with paclitaxel. So I have to say that it was, I think, overextending -- I think you will get "rare adverse events," and I think you're going to need a prolonged five-year follow-up with several thousand people to be able to make any sense out of rare adverse events.

DR. PAGE: And we will address whether you think that that is so important that it could be addressed in a post-approval, or whether you consider this approvable, but we will have that discussion.

DR. SOMBERG: I can tell you now, I would do post.

DR. PAGE: Thank you.

Any other comments?

Yes, Dr. Simon.

DR. SIMON: I would just say, for a device study, I thought these

numbers are very good. It's not a drug study where they enroll thousands of patients. But for actually a device study in interventional endovascular therapy, these are robust numbers for enrollment.

DR. ZUCKERMAN: Okay, but Dr. Simon and the rest of the Panel, we would say for a combination product study because we do have to respect that there's a drug here. And, certainly, I'd like Dr. Somberg to respond. You know, we do have paclitaxel use in the coronary arteries, as a treatment for breast cancer. Does that make you any more comfortable?

DR. SOMBERG: Well, I'm not uncomfortable. Don't misunderstand. And I'm not suggesting to any of my colleagues here that that should be the basis because we have an inadequate sample. That should be a basis for a negative decision. But the concentrations here are higher than what you're giving in the coronaries. And I think you will use more than one balloon, so you will get higher concentrations.

But I did see those pictures, and I am a clinician, and therefore, what happens in a rare instance many years down the road has to be balanced against people losing their extremity and having severe infections and dying of sepsis. So with that said -- and I wasn't saying we should approve or not approve, but all I'm saying is that if this was approved, a post-approval surveillance is certainly needed given the inadequacy of the data. That's all.

DR. PAGE: Other comments from the Panel?

Dr. Cigarroa.

DR. CIGARROA: I would certainly comment that the coronary literature, given the concentrations used and the time of elution and the use of the different polymers, doesn't make me feel good in terms of comfort level; however, the use within the cancer population does. And I think that we certainly know a lot about the systemic effects of this particular agent. What we don't know is the direct issues within the vascular wall in an atherosclerotic human peripheral vessel. But I'm less concerned about that.

DR. PAGE: Great.

So if I may, Dr. Zuckerman. First of all, excellent safety is demonstrated and the numbers in terms of negative outcomes are very small or zero. The number was not reached that FDA had at least thought was agreed upon, and I'll comment on that in a moment. And in terms of certainly a drug study, which this kind of is, the numbers are not as large as we expect in large drug trials. How to address that, I'm getting a sense that that might be considered at a post-approval study, but we'll see how that goes in terms of the rest of our deliberation.

My comments to Dr. DeFord -- and I'm satisfied by his response. But I do encourage, in the future -- I may be sitting here in the future -- that the conversation be maintained between the Sponsor and the FDA as to what's expected before a PMA is allowed. And if a number of safety patients enrolled is expected, then I think the Panel ought to expect

that the Sponsor will abide by that if it's made adequately clear and the conversation is ongoing between FDA and the Sponsor.

But back to the issue of Question 3b, I've given you the response, and that is that the sense is that safety appears to be excellent, but we really don't have the numbers in terms of a long-term drug study, although some comfort is provided by the concentrations provided in the oncology world and not the coronary intervention world.

Is that satisfactory?

DR. ZUCKERMAN: Okay, that's an excellent summary. And I'm glad you made the last comments, Dr. Page, because various members of the drug coated balloon industry are in the audience and will be looking at the transcript. And to further underline the seriousness with which the Agency takes the safety issue, when other drug coated balloon PMAs are filed in the future, we'll be looking more specifically at the safety numbers. So, please, for other industry sponsors, listen very carefully to Dr. Page's sage advice.

DR. PAGE: Thank you.

Let's move on to Question 4, looking at effectiveness. The primary endpoint for effectiveness is primary patency, defined as freedom from target lesion restenosis (per the core lab adjudication with the binary cutoff of 2.5) and target lesion revascularization. There is a table here on pages 3 of 9, and there's also a discussion, again, about this ITT versus PP.

Ms. Pack, would you please read Question 4a?

MS. PACK: Question 4a: Given the imbalance of missing data between the two treatment groups, please comment on the difference in the findings for the intent-to-treat and per-protocol analyses."

DR. PAGE: Thank you.

We've had some discussion about the PP versus ITT. I'm interested in at least a Panelist or two commenting about their perspective. If it's identical to our discussion on safety, that's fine, but I do think we should hear from the Panel. And then I'll look around, and see if there is consensus, I will summarize for Dr. Zuckerman.

Dr. Somberg, thank you.

DR. SOMBERG: I would just say it was very similar to what we were discussing on safety, and there is, once again, a modest difference in effect size, and we don't see that with the per-protocol analysis. But somehow it's reassuring. And what hasn't been said is that the ITT and the as-treatment analysis are the same. And when you have a non-inferiority study, it's the on-treatment analysis that should be given priority, not the intention-to-treat, which was at first thought to be the primary and only thing one would look at. So I think now that the intent-to-treat and the as-treatment analysis is similar and we have good reason to believe that the per-protocol takes us into swampy territory, we should be less concerned.

DR. PAGE: Fair enough.

Dr. Lange.

DR. LANGE: Could I ask a clarification from the FDA? In terms of effectiveness, if the definition is or if the indication is to improve patency, not to be better than current therapy, but to improve patency -- in other words, are we trying to prove superiority or similarity?

DR. ZUCKERMAN: Okay. We have, with this particular device, an added component compared to a very acceptable control, which is PTA. And that's why the Sponsor appropriately chose, with the added risk of adding a drug, a superiority analysis. And certainly the primary endpoint analysis, which was the ITT, was met. Now, we can debate as to what the meaning of that trial effect is on a clinical basis, whether it's patency or clinical symptoms or whatever, but I do think we need to recognize that the agreed-upon primary endpoint between the Sponsor and FDA was clearly met.

DR. PAGE: And just to be clear, that was superiority over standard of care.

DR. ZUCKERMAN: Correct. And the superiority hypothesis was chosen because we have the effect of an added drug, and we wanted to show that the combination product was doing something in toto.

DR. PAGE: Dr. Posner.

DR. POSNER: Yes. Just to clarify, for me. I've been looking at this. It's not just patency; it's prolongation of patency. Because you're getting patency by the first balloon going in. And since this balloon, at least

in their presentation, never adds pressure to open up the lumen any further than the original opening; it adds the drug and it's the drug that's supposedly prolonging the patency, not actually causing the patency. And I may be wrong, I mean, but that's --

DR. PAGE: I think you raise an interesting issue, and they were all patent essentially after the procedure. But what is being measured is patency at 12 months, and so in that case, they were all patent to begin with but more were patent, about 12.5% more were patent, at 12 months. So along that line, I'm interested -- I'll call on you in a second, Dr. Cigarroa -- in terms of, as we're discussing the endpoint being met, I would just like to hear from the Panel as to the issue of clinical significance. I've heard Dr. Hirshfeld call this modest in terms of the effect. Is it clinically important to have a 12% greater likelihood of being patent at 12 months?

Dr. Cigarroa.

DR. CIGARROA: So the clinical significance of patency, that is you can have a percentage who meet the binary definition of restenosis who are 55% and asymptomatic. We saw that. And so, really, the significance comes down to does that result into a functional change for your patient with regards to quality of life or morbidity? And the answer to that appears to be modestly yes. And so I think it becomes clinically significant from the patient perspective, and it's of modest effect.

DR. PAGE: So if I may, Dr. Zuckerman, with regard to Question

4a, the feeling about the ITT and the per-protocol is similar to before. The ITT and even the on-treatment being the same and having the positive efficacy endpoint, carries the day in terms of the Panel.

In terms of the outcome, is it statistically significant? Yes. And is it clinically relevant? I'm hearing from the Panel that it is moderately or modestly clinically important, but if you're in that group that's benefiting, I think, overall, the committee is saying that this is a clinically relevant endpoint that has met statistical significance.

Is that helpful?

DR. ZUCKERMAN: Yes. This is a tough dataset to look at, and I would just like one additional piece of clarification from Dr. Cigarroa because I think he framed his conclusions very nicely.

When you see that modest clinical benefit, is that primarily based on the forest plot of additional clinical endpoints that the Sponsor showed that seemed to all trend in the right direction, or can you be a little bit more specific?

DR. CIGARROA: So the answer is yes and yes. So the concordance of trends towards improvement certainly help framed things for me. The second aspect of it is the fact that revascularization, that is repeat procedures, occurred less frequently in the overall intention-to-treat group is a meaningful endpoint to a patient. It is time, it is morbidity, it is financial impact. And so I think it's a combination of those two.

DR. ZUCKERMAN: Thank you. That's very helpful.

DR. PAGE: And if I may, I might comment that just as I was respectful about the agreement between the Sponsor and the FDA, the number in the safety trial, likewise, when this was being mapped out, the composite primary endpoint was agreed upon with FDA and the Sponsor, and that included both a clinically relevant endpoint, which is the TLR, and frankly, a surrogate endpoint in terms of symptoms, which is the restenosis. And it's not our job to rewrite the indications for the entry and the primary endpoint; it's too late for that. But wouldn't you say that people don't come in to their doctor complaining about reaching 2.5 for their ratio? But the FDA was satisfied; the Sponsor's consultants, I presume, were satisfied; and I'm getting a sense of general satisfaction from the Panel that this is a reasonable endpoint, especially in combination with the clinically measurable endpoint, and that is TLR.

DR. ZUCKERMAN: That's a good summary of the history and present situation.

DR. PAGE: Dr. Hirshfeld.

DR. HIRSHFELD: I think another aspect of understanding some of the statistical near misses in terms of significance, if you want to call it that, are if you go back to the parameters that were taken when the study was designed. And so the Sponsor designed the study anticipating a 59% success rate in the treated group and a 42% success rate in the control group.

And what they got, for the treated group, instead of 59 was 65, so they did better than they expected.

They also -- the control group did substantially better than expected. It did 52% instead of 42% and so the difference was smaller than was expected in the initial study design and that's the reason that the p-values all came out to be closer than they wanted, and as soon as you lose more patients from the study set for other types of exclusions, then the statistical significance fails to meet the endpoint.

DR. PAGE: Fair enough.

Dr. Lange.

DR. LANGE: Again, just an encouragement to the FDA. And, again, I don't want to change the rules. The rules are patency. When I look at every clinical measure, only one fell out. I mean, there are several. The walking improvement questionnaire had to do with pain, which is negative; walking speed score, stair climbing score. The six-minute walk test was negative. The EQ-5D was negative, the SF-36 Version 2 was negative.

I mean, all the clinical parameters that we use to gauge whether we're making the patients better or not, it didn't get better except for one they just pulled out, and that was how the patient assessed how far they walk. Now, when they put them on a six-minute walk test, they didn't do any better. I hate to do a procedure just because someone has a predetermined test result, a velocity of x. I would prefer to think I'm either

improving their survival or improving their symptoms.

DR. ZUCKERMAN: Those are excellent points, but can you help us? I don't know which page you're on. When you say they didn't do better, they didn't do better from a statistical p-value or was the trend reasonable? Or how are you defining not doing better?

DR. LANGE: I'm looking at the Sponsor's material, and it starts on page 101 and travels all the way through -- it's the page numbers 101 through 105. And by the way, kudos to the Sponsor. They just put it out there. They didn't paint over it; it is what it is. It just wasn't one of the prespecified -- but the Sponsor is very honest about it, where there was no -- there were small differences. And there was only one that fell out.

DR. PAGE: Dr. Lange, just so I'm clear. And certainly those various secondary endpoints were not met, but in terms of the forest plot that was shown with everything kind of going that direction but the whiskers overlapping no effect. Did you find that compelling at all?

DR. LANGE: No, no. When I try to go home, if I just kind of head in the right direction, I seldom get there, okay?

(Laughter.)

DR. LANGE: So heading in the right direction doesn't quite cut it.

DR. SOMBERG: Can I just add something to this?

DR. PAGE: Yes, Dr. Somberg.

DR. SOMBERG: Well, what I think is this all underscores the modestness of the effect. If it was much larger, we presume, at least I presume, that when you increase the luminal diameter and you prolong its maintaining that, then the clinical effects would follow. But since the clinical and the luminal diameter effects are modest, you need a larger sample size. So the whole problem relates to first principles. The sample size was too small; the estimates were under or over. Actually, it's the other way around. They were over-enthusiastic, and we have what we have.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: Nothing further.

DR. PAGE: Is that because you agreed with Dr. Somberg?

DR. CIGARROA: Yes, because I agreed.

DR. PAGE: That's what I just wanted to find out.

Dr. Lange.

DR. LANGE: I don't. It's okay. And Dr. Hirshfeld pointed to this before. We used to use binary lesions to define restenosis and coronaries. So if you're 51%, you're restenosis; if you're 49%, you weren't. There was no difference in the symptoms at all. And that's why I think if you just use -- you can say it's more patent because you were 51% and 49%, but it doesn't translate into a better clinical benefit.

DR. SOMBERG: You're putting words in my mouth here. We're not at 51 and 49. We're at, what was it, 65 and 52. So we have a much

bigger spread here.

DR. ZUCKERMAN: Okay, let's --

DR. SOMBERG: If it was 49/51, very few people would be going this way, they would be going --

DR. PAGE: Gentlemen, let's hear from Dr. Zuckerman.

DR. ZUCKERMAN: Let's take a time out because I think this has been a very healthy interchange. You know, ultimately each Panelist will have to deal with the data in their book and figure out the benefit/risk profile. But I think this problem, again, gets back to one that we see time and time again at these panels and was underlined superbly by Dr. Somberg. The sample size guesstimates that most sponsors start with in the device world are bizarre. They're wildly optimistic.

Now, I can appreciate why people are optimistic in the device world, but certainly there are better methodologies to use, in general, and this Panel has seen them, and they include a matrix of less optimistic sample size guesstimates, a consideration of a group sequential design with early stopping, or an adaptive sample size type trial where we can enlarge sample size. But this is the problem that the industry continually gives you folks, and I hope that we can see some changes because the clinical trials methodology is much more advanced right now.

DR. PAGE: Thank you, Dr. Zuckerman. I summarized 4a and then we kept talking. Do you need a further summary of this second

conversation, or are you satisfied?

DR. ZUCKERMAN: No, I think the conversation was excellent and just underlines the complexity of the situation that Panel members are dealing with.

DR. PAGE: I agree.

Dr. Ohman, are you on the phone, sir?

DR. OHMAN: I am indeed, Dr. Page.

DR. PAGE: I know you've been listening, and I know you would have told me if you had to speak, but I want to make sure we're hearing from you. Are you comfortable with the comments and the summaries? I don't get to see whether you're nodding your head there in North Carolina.

DR. OHMAN: I was trying to nod my head very forcefully so you could see it. I had to agree with what has been said about the indication for use. I would agree with the approach taken for the safety. I believe the device has proven safety. And the efficacy, I would lean towards seeing it in totality of data rather than a particular subgroup.

And in response to Dr. Lange's commentary, I think while it's useful to head in the right direction, you will eventually find your way home if you head in the right direction and things are heading predominantly in the right direction. I think it points to the right piece. There's no red alert as far as the overall efficacy piece.

DR. PAGE: Thank you, Dr. Ohman.

DR. OHMAN: I hope these comments will help.

DR. PAGE: Dr. Lange has to say something.

DR. LANGE: Dr. Ohman, I respect your opinion tremendously, but talking about the right direction when you're sitting in North Carolina right now, it's --

(Laughter.)

DR. PAGE: Point well taken, Dr. Lange.

DR. OHMAN: Point well taken.

DR. PAGE: Okay, moving on.

4b is regarding the second table on page 4 of 9, and it's looking at total TLR at 12 months. This is a secondary endpoint in and of itself, but I remind the Panel that it's a composite in our primary efficacy endpoint.

Ms. Pack, would you please read Question 4b?

MS. PACK: Please comment on the clinical significance of this finding (i.e., no statistical difference in the occurrence of TLR at 12 months between PTA and the Lutonix Drug Coated Balloon) or any other observations regarding the secondary endpoints.

DR. PAGE: Thank you.

Comments from the Panel, please.

Dr. Lange.

DR. LANGE: Again, I'm a little confused because I'm not sure what TLR -- because it wasn't symptoms; it was just based upon a binary

restenosis definition. If it was restenosis, they got TLR. And it's moving in the same direction as everything else.

DR. PAGE: No, I think -- I'll call on you, Dr. DeFord, if we need to. But TLR was, by definition, a symptom-driven event. That's my understanding. Am I correct? Looking at the Panel.

Is that your understanding, Dr. Cigarroa?

DR. CIGARROA: My understanding, as it was presented, is that the clinician caring for the patient at 12 months, or whatever time point the patient was evaluated, made a decision based on the patient's examined symptoms, not based on the ultrasound.

DR. PAGE: And then subsequently the DUS results were made available.

DR. LANGE: Thank you for the clarification.

DR. PAGE: So, in that setting, are there other comments? Are people troubled? Let me just ask a question. We have a p-value of 0.21, so it didn't meet statistical significance. We've been talking about -- well, it was always a secondary endpoint, but it was a composite of the primary endpoint. Do people have concerns about this?

Dr. Cigarroa.

DR. CIGARROA: Well, to me, it's the most important endpoint, and that is, from a patient perspective, what do they expect? And I would say they would expect an improvement in quality of life, they would expect an

improvement in limb salvage and that is freedom from amputation, and again these numbers are relatively small, 17% to 12% heading the right direction, but statistically not significant. So I think it reflects the modest impact that adding the drug has to the balloon. So I am troubled, but accepting.

DR. PAGE: I'm looking at nods from the Panel.

So if I may, Dr. Zuckerman, with regard to Question 4b, this is seen as a composite that helped drive the statistically significant, clinically relevant, modest effect of the intervention, and it is acknowledged as a secondary endpoint that's going in the right direction. And the fact that it doesn't have a p-value of < 0.05 reflects a number of issues, low instance and relatively small population, but we see this as an important finding and of clinical significance.

Does that help?

DR. ZUCKERMAN: Yes, thank you.

DR. PAGE: Moving on to an area that took a fair amount of discussion -- and I'm going to try to limit the discussion about Question 5, but make sure that we get our job done properly -- on geography and gender subgroup analysis. And I've got to thank and acknowledge the statisticians from both the FDA and the Sponsor for going through more permutations of sub-analyses than I think I've ever seen in terms of trying to explain some puzzling results. So I would draw your attention to the table on page 5, the table on page 6.

And I will now ask Ms. Pack to read Question 5a.

MS. PACK: An interaction with geography was observed for both primary safety (p=0.02) and primary effectiveness (p=0.12). Based on the three-way interaction test for geography, gender, and treatment group, these differences in geography seem to be related to the differences between the U.S. and OUS female (p=0.001 and 0.10 for the primary safety and the primary effectiveness endpoints, respectively). Please comment on the poolability of the OUS and U.S. data given these results and what impact, if any, this may have on the need for additional U.S. data post-approval.

DR. PAGE: So I'm going to call on Dr. Naftel because he, in part, asked, I believe, one of the statisticians as to whether FDA thought this was poolable, and I would say that I'm not sure everybody at the FDA agrees one way or the other in terms of that question. But it comes down to us, so I'm interested in your comments as to, first of all, whether the data are poolable and also what you're taking from the various analyses outside U.S. -- female, gender -- and then further on down, even including smoking.

Dr. Naftel, do you care to comment?

DR. NAFTEL: Yes. So this is really difficult for me, I just have to admit, because I totally believe in creating a clinical trial to answer one question or two questions. I mean, that's what I believe in. But I've also been trained by FDA on the whole issue of poolability. There are actually three issues: one, whatever the groups you're looking at. This case, U.S. and

outside U.S.: (1) Do they follow the same protocol? (2) Do they have the same baseline characteristics? And then the last thing, do they have the same results? So, for poolability, we've got (1) and (2) without any problem from what we've read. So poolability is fine. But then we get to the real thing, the results, and I am just uncomfortable.

I believe, I'm sure all of you have read the books by Sir Ronald A. Fisher, the granddaddy of modern statistics, where he says you have to look at recognizable subsets where you have an obligation, as an analyst, to look for things even if they aren't preplanned. So we have that on one side; we have the clinical trials on the other where we just have one question.

I think we're in a very uncomfortable spot, and I think I personally am going to push, in the future, for FDA and the sponsors to do a better job in designing experiments to answer these two questions that are always there: female versus male, outside versus inside the U.S.

I'm not going to philosophically punish this clinical trial for what should have been done up front, so I'm going to go with saying yes, it's poolable, and yes, I'm going to look at overall results. But I hope that Bram lets me continue to be a Panel member so that I can push to address these two issues in the future.

DR. PAGE: Thank you very much.

And, Ms. Chauhan, I'll be calling on you in just a second.

Ms. Pack, go ahead. I'll take the liberty of reading Question 5b,

because these two are really intertwined. Or why don't you go ahead?

MS. PACK: Certainly. Please comment on the clinical significance of the observed differences in outcomes between males and females, as well as the U.S. and OUS females.

DR. PAGE: Thank you. Because we really need to take this together.

Ms. Chauhan, Dr. Cigarroa, and Dr. Somberg.

MS. CHAUHAN: Dr. Naftel, I have a question for you based on --

DR. PAGE: Can you speak up, please?

MS. CHAUHAN: Oh, I'm sorry.

I have a question for you based on what you just said. You said of three areas, it met two. I'm not a statistician at all, but when I was looking at the things they put up after lunch, it seemed to me -- because at first, I was struck by the paradox that the smokers in non-U.S. did better than the nonsmokers here. But then when I looked at the other stuff they put up, it seemed to me the two groups on comorbidities were very different. Does that not mean anything?

DR. NAFTEL: Absolutely. Like I said, all the groups had the same protocol, same definitions, baseline stuff pretty much the same. But you're right, there are some inconsistencies in the results in even funny ways. I don't like to dig down too deep in this. I'm willing to look at U.S./non-U.S.,

male/female. When I start getting to the smokers and all, then I feel like I'm on a little bit of a treasure hunt, although the results were incredibly interesting.

MS. CHAUHAN: What about the comorbidities? You put that with the smoking.

DR. NAFTEL: It just bothers me, but that's really all I can say.

MS. CHAUHAN: And the racial divides were different, too.

DR. NAFTEL: Um-hum.

MS. CHAUHAN: I just think that's really important information when we -- as you said, when you're developing trials, that these things need to be taken more seriously, especially because the United States is a far more racially diverse population, and then I think you get into genetific things. And it bothers me.

DR. NAFTEL: And I agree. And I have the impression that the U.S. females were actually considerably sicker --

MS. CHAUHAN: Yes.

DR. NAFTEL: -- than the European, that's really what you're saying. And so that increases my discomfort because you're right, U.S. citizens are different from European; there are lots of studies about that and they are different. So I am uncomfortable, but I'm still going to go with the clinical trial mentality.

DR. ZUCKERMAN: Okay. Ms. Chauhan and Dr. Naftel, you've

had an excellent discussion, and I think that you're more in agreement than disagreement, but I would like to get the clinicians' focus on this critical question. And to do that, I would like them to look at the forest plot labeled CO-72 on page 16 of the Sponsor's slides, because in the end, as Dr. Naftel has indicated, the U.S. female population that received the drug coated balloon didn't do well. And, certainly, Dr. Naftel has pointed out some basic principles that the FDA uses, which is, number one, we have to look at these important subgroups carefully. We have to use interaction tests, as you've heard.

But the second component that he pointed out is we try to reduce the probability of these problems occurring at panel by better trial design. And certainly the FDA accepts responsibility, as well as the Sponsor, for what we have here. But that doesn't reduce our need to look at the data right now and to try to interpret it in the most correct clinical light.

And that's where we need the help of the clinical trialists, because in addition to the statistical argument raised by Dr. Naftel, which is one powerful tool we use, we have to try to put this in a clinical context:

- Is it reasonable?
- Is there biological plausibility?
- Have we seen these results replicated in other studies?

So we have to take a view here where I need some clinical expert commentary right now.

DR. PAGE: Thank you.

And I know Dr. Ohman is on the phone. And I see Dr. Cigarroa and Dr. Somberg, as well.

Dr. Ohman.

DR. OHMAN: Yes. So thank you for asking me, Dr. Page.

I have to agree with Dr. Naftel that the challenge here is the sample size is modest and therefore spurious interaction can occur with the p-value. That is significant. One of the reasons I asked what really drove the primary endpoint in the discussion, and I think I got it right when it was explained to me, was the fact that the main driver of the primary efficacy endpoint was smoking status. With that in mind --

DR. PAGE: Can you say that again, please?

DR. OHMAN: Was smoking status.

And correct me if I'm wrong, because I was never able to see that slide, but from what I can gather, this was the main driver of the efficacy endpoint. That is to say, it was the variable that was most closely associated with the outcome of the study from an efficacy point of view. If that's the case, then if I see something in women plus/minus smoking, I might actually assume that this would be spurious because the main driver for the outcome might be smoking. So that's only one aspect of this; therefore, women who smoke or not smoke is a relatively small subgroup where you could potentially see a spurious effect with no biological activity. So that's one

commentary on this.

The second is that we've seen this in trials over and over again. And I'll just bring back, for those of you who remember, the ISIS trial that showed a very highly significant reduction in overall mortality. Of course, it was 20,000 patients; we have a little bit more to go by. But in that trial, the birth sign Gemini had zero treatment effect, and basically, the trial with that subgroup was entirely neutral. That is to say streptokinase did not lower mortality whatsoever. Yet, we know, from the overall trial, that it was a highly statistically significant finding.

So, in summary, my bias would be to accept the overall statistical finding of the overall analysis and allow subgroups to be explored in some fashion when it gets out in the market because it may be that the factor is not women but actually smoking status that drives this small subgroup.

I hope these comments help.

DR. PAGE: I'm hoping other people could hear you better than I could, Magnus. I'm sorry.

Joaquin, do you mind just summarizing what Magnus -- the last two sentences that he said and give your perspective, as well?

And then Dr. Somberg and then Dr. Lange.

DR. CIGARROA: Sure. I believe he stated that given small sample sizes, there are challenges in interpreting the individual dataset for

the in-U.S. versus out-of-U.S. women, that he hopes that in future data follow-up that that may be elucidated, and that he would go ahead and recommend proceeding with the overall ITT results.

I would comment, as well, from my perspective, that the U.S. women are fundamentally different with regards to comorbidities. And we do know that the comorbidities can influence subsequent restenosis rates and progression of clinical disease, specifically, substantially greater percentage of diabetics. A much higher overall burden of atheroma is evidenced by a substantially greater number of individuals having been diagnosed previously with coronary disease, previously having undergone coronary revascularization procedures, previously having experienced cerebrovascular accidents, and a greater number of lesions that were restenotic relative to de novo compared to the European cohort.

And so I would agree with the group included, but there are signals here that in a higher atherosclerotic burden, higher comorbidity, that what is a modest treatment effect in the overall cohort may disappear, and I think that should be elucidated in the future.

DR. PAGE: Fair enough.

Dr. Somberg.

DR. SOMBERG: I'm agreeing with Dr. Cigarroa. I think women in the U.S. showed such a diametrically opposed trend than the overall finding that we have to take note of it. And, therefore, I'm not sure where

this should be, Bram, in the indications and the overall insert, but I think there should be a warning that in women with severe disease, efficacy of the DCB has not been established. If we decide to recommend approval, I think I would have to say that, in that subset, even though it's difficult to say and we have all sort of qualms, the data -- we have to be very cautious that we're giving a lot of allowance here, and the trend is very much diametrically opposite.

DR. PAGE: I'm looking for other Panelists as to whether you would agree, and in carving out populations who were included in this study in terms of the indications.

Dr. Posner.

DR. POSNER: Well, I'll just repeat what I said before, I think. Each group has had people that have benefited. Each group has had people that haven't benefited. And until the numbers get large enough to make the statement that women aren't benefited, you can't say anything definitively, and particularly since the women are not a single group. The European women smoke Eastern European tobacco without filters; the American women smoke filters. You talked about the number of diabetics, et cetera.

I don't think you can make any decision. And my point would say is if the data shows that people are being helped with this, then go on and let them try it and gather the numbers. And at the end of a year, five years, when the numbers come up, then look at the data and say, well, it really

doesn't help women that have diabetes or have coronary artery disease or have hypertension.

DR. PAGE: Thank you.

Mr. Thuramalla.

MR. THURAMALLA: I would like to summarize and add to what Dr. Ohman and Dr. Posner just said. I think looking at the totality of the ITT -- I think we agreed that there is superiority. We also agreed that there is non-inferiority in terms of safety. And we also agreed that at best, it can be considered modest. So by dividing into subgroups and groups underneath it, it is only going to add confusion. But I agree with Dr. Posner that we should -- if we agree this is effective and non-inferior in terms of safety, then it should be allowed to be used, and post-approval study may have to focus on these elements to better bring light onto these aspects.

DR. PAGE: Thank you.

DR. ZUCKERMAN: Let me respond to the last three comments because this discussion has been excellent, but I'm sure Dr. Page needs to wrap up.

Dr. Somberg, generally the FDA, in our label, wants to be fully transparent. And as you know, whether in drugs with the MERIT heart failure beta blocker trial or in this particular instance, there wouldn't be a problem with putting the results in as we have them and trying to explain, as you indicated, that these are the results and we can't fully explain them at this

time.

But, Dr. Posner, all through today you have indicated that we need larger numbers, larger number of women, a better gender study. I would just point out to the Panel that enrollment and design of that post-approval study has not been begun by the Sponsor, and so when you get to that point which asks about the adequacy of the post-approval study, I think that's the point where you need to further consider your suggestions. So like in many trials, we are left with questions, but is this a rate limiting question?

And perhaps Dr. Page can sum up.

DR. PAGE: Thank you.

If I may, I would summarize this as the group, overall, accepting poolability -- although statistically there may be concerns, these are the data we have. In terms of the OUS, the women, the smoking, everyone is concerned and can't really explain necessarily, although we've tried a number of gyrations with the data to explain some of the things we're seeing. But we're agreeing that we need more information and, if nothing else, in a long-term follow-up post-approval way that would be made available.

There may be some concern, but I don't believe it's the majority, as to whether one can label this for women. I think the majority would say that it would be labeled for the population that was studied, but the data would be included along with the product to make it clear to whoever is using the product that there are these issues that are of some

concern.

Is that satisfactory, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Great, thank you.

Let's go on to Question 6, long-term follow-up. You see the data on page 7 of the packet, and we have discussed this at some length.

Ms. Pack, would you please read Question 6 for us?

MS. PACK: Please comment on the adequacy of the amount of long-term follow-up data collected, keeping in mind the observed diminished treatment effect at 720 days.

DR. PAGE: I'm looking to the Panel for any comments about long-term follow-up. This is a secondary analysis.

And Dr. Lange.

DR. LANGE: Just in short, I think there is inadequate information to gauge long-term follow-up, so I'm very uncomfortable saying there's diminished -- maybe a subset -- diminished treatment effect. I don't think we can make that comment.

DR. PAGE: So when you say you're uncomfortable, you're uncomfortable with regard to this, as to this being unacceptable in terms of safety and efficacy? Or are you uncomfortable that you'd like to gain more comfort with long-term follow-up? If you don't mind commenting.

DR. LANGE: We don't have enough -- the patient follow-up that

extends past one year is small, it doesn't extend to 720 days. We don't have a big enough patient -- to say there's diminished treatment effect. So we just don't have that information.

DR. PAGE: Fair enough.

Dr. Somberg.

DR. SOMBERG: It's sort of fundamental to a number of questions we have because we don't have the data. We have to guide people. No one's going to go through the data packs like we do. I mean, most interventionists want to use something, not to spend three or four nights reading something on this. I'm only kidding.

But, in actuality, I think because we do not have the data, we should say long-term durability of effect has not been established, just as we should say something about we do not have established -- in women, because we don't have it. I think it should be stated out there instead of bury -- I don't mean to say people will try to bury it, but it will be buried in a large data report as opposed to succinct statements.

DR. PAGE: I might question the use of buried in terms of -- as Dr. Zuckerman said, the FDA will make every effort at transparency. But you are expressing concern that just how transparent -- we will be very transparent about issues, certainly with regard to the absence of long-term data and you brought up your previous concern about women. Is that correct?

DR. SOMBERG: I'm just saying instead of just being transparent, we have to be affirmatively active in pointing out certain critical areas that may raise clinical decision-making issues like durability of effect and like gender-specific problems. And just one subset of that. I think the gender-specific problem is -- we spent a lot of time on tobacco, but they had much more severe disease. And I think that may just be the answer.

DR. PAGE: Dr. Posner.

DR. POSNER: Just to point out that in a long-term study, if we started out with too small a set of numbers, the numbers are going to fall off with time, so if we weren't happy at the beginning, we're certainly not going to be happy at two years. And it's going to be even worse at three years. And so the answer is what Dr. Zuckerman suggested: If this is approved, we continue collecting data as people start and following on. And so we'll have a pooled number of one year, two years, three years, five years, six years, and over time we will get sufficient numbers to say something. But, clearly, the long-term data isn't any better than the short-term data and, in fact, it's worse because people have dropped out.

DR. ZUCKERMAN: Right. I'm sorry, Dr. Page.

DR. PAGE: Ms. Chauhan had her hand raised.

DR. ZUCKERMAN: Sorry. Ms. Chauhan.

MS. CHAUHAN: I just want to support what Dr. Somberg said because I think it's really important to remember two things. These are

human beings' lives we're talking about, the women, all of them, but the women who are at issue. And we might like to think everyone reads the whole insert pack carefully, but they don't. That's human nature. They're going to read what they see as the important stuff, and I think this is part of the important stuff.

DR. PAGE: May I press you on that just for one moment? And that is, as our representative, as a Consumer Representative and a woman, you're hearing from Panelists a variation as to whether they really believe there's a signal that this doesn't work for women.

MS. CHAUHAN: Right.

DR. PAGE: Would you want to steer doctors away from using this on women in the United States if it's available?

MS. CHAUHAN: At this point, yes. Because I go back to, first, do no harm. And I think these, as you pointed out, are much sicker women. And so if they want to do it on women in the United States, then they need to make sure that their health level is equivalent to the health level of the women in Europe. Make it a level playing field, if you will.

DR. PAGE: And I thank you for your input. I will mention that a number of us who sit on these panels very often -- there's often a group that when you carve things out, appears that it's less effective, and one of the concerns that all of us have to balance is a very good point you're making, balance with the idea that if this truly improves patency, to keep women from

having it because of a statistical quirk that does not necessarily meet statistical significance is what we're balancing.

So, as we go through our decision, if people seem like they're not necessarily following your guide in terms of the issue of women, it's also that we're wrestling with the fact that I don't want to keep a smaller group from having important therapy, if we indeed decided that was important therapy.

MS. CHAUHAN: I didn't have any sense you weren't following my guide.

DR. PAGE: No. No problem.

MS. CHAUHAN: I have sense that the Panel is really struggling with this issue, and so I want to be sure that this point has support; it's not just one voice.

DR. PAGE: You bet. Thank you very much.

MS. CHAUHAN: Okay.

DR. PAGE: Dr. Zuckerman.

DR. ZUCKERMAN: No, I want to underline the importance of Ms. Chauhan's statements. And the Panel will really need to decide, with the final vote, whether this is an all-inclusive therapy or there are major holes here. I would also like to respond to Dr. Somberg's excellent point about the Agency needing to actively acquire needed data.

Again, I would point you to either the options of (1) just

deciding that necessary data are not currently found in this Panel Pack, or the option of designing a post-approval study that can better answer the question of how these patients do long-term, including how they do when they are re-treated, either with drug coated balloon or standard PTA. There are a lot of important questions that have been raised in this Panel discussion right now that are not currently in the post-approval study design, if that's the option that the Panel wants to go.

DR. PAGE: Great, thank you.

So to get back to Question 6, I think there's consensus that there aren't adequate long-term safety or long-term data available at this time, but we have what we have.

Is that acceptable, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, that's a very good summary.

DR. PAGE: Dr. Hirshfeld.

DR. HIRSHFELD: Can I ask one question for regulatory information? So we have a statistically significant effect at 12 months. The effect is diminishing with the data that we have by 24 months. If the device is approved and the subsequent 24-month data come in and show loss of effect at 24 months, what are the ramifications of that finding?

DR. ZUCKERMAN: I think you need to think about the overall picture or the current totality of the data when you put together your overall risk/benefit profile and think about how you're going to vote, Dr. Hirshfeld

and other Panel members. The only thing that I would say is that as opposed to a permanent implant, i.e., a stent, this is a balloon procedure, and you can think about how that might affect your benefit/risk profile given that durability is well summarized by Dr. Page's last statement.

DR. PAGE: Okay, we'll move on to Question 7, evaluation of the totality of the data from the Lutonix DCB trials and examining the overall benefit/risk assessment. Let's go ahead and have you read 7a, b, and c. And I'll ask to handle them one at a time, although they may significantly overlap.

Ms. Pack.

MS. PACK: Question 7: Please comment on what the totality of the currently available data suggest about the benefit/risk profile of the Lutonix DCB device. As part of this discussion, please comment on the following:

a. Please comment on any concerns raised by the failed per-protocol analyses considering that both intent-to-treat analyses were successful.
b. Please comment on whether an equivalent rate of TLR between standard PTA and the Lutonix DCB is clinically acceptable given the improvement in Primary Patency associated with the Lutonix DCB.
c. Based on all of the information presented in the Panel Pack and discussed here today, please comment on whether the safety

and effectiveness results from all available LEVANT 2 studies indicated that the Lutonix DCB device is a clinically acceptable alternative to standard balloon angioplasty.

DR. PAGE: Thank you, Ms. Pack.

If I may, Dr. Zuckerman, and if the Panel will permit me to, I think we've already addressed (a) in terms of the issues of what's called the failed per-protocol analysis. We talked about this in terms of safety and effectiveness, and I think you have enough conversation already in the record that documents the fact that the ITT and the as-treated were what was compelling to us, and the per-protocol, not.

DR. ZUCKERMAN: I agree.

DR. PAGE: Great.

Moving on to (b), I think we're there, but the Panel can correct me if I'm wrong, in terms of the TLR. I would actually have a bit of a problem with the question saying they are equivalent. There was certainly a difference in TLR between the two that did not reach statistical significance with a p-value of 0.21, I believe. But we have discussed that, and that was seen as potentially a clinically important finding that contributed to the primary endpoint, although in and of itself, it was a secondary analysis that did not reach statistical significance.

I'm looking around at the Panel to see if they agree I've summarized adequately, and I'm seeing nods. And if so, is that satisfactory,

Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Good. Then let's go on to 7b [sic]. And here I will ask the Panel to be fully engaged in Question 7c, and that is putting together safety and efficacy, whether this is a clinically acceptable alternative to standard balloon therapy or, as Dr. Cigarroa pointed out, additional therapy on top of balloon therapy.

Joaquin, I'll ask you to kick off the conversation.

DR. CIGARROA: So as an adjunctive therapy, with all of the limitations of the sample size and the subgroups, I believe that (a) it is safe, and (b) I think it is modestly effective in reducing the composite endpoint, as designed.

DR. PAGE: And then from your standpoint, as such, is it a clinically acceptable alternative to plain old balloon angioplasty?

DR. CIGARROA: Adjunct in addition to PTA.

DR. PAGE: Great, thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yes. And in addition to what Joaquin pointed out, I think considering the alternative, considering this population, with all the limitations that we've discussed, I think that it's hard not to consider that when balancing the effectiveness and safety and thinking that it would be a reasonable adjunctive therapy for this population.

DR. PAGE: Great, thank you. And as I posed the question, if I might expand it a little bit, and again, this is discussion regarding the indication with the modification of it being post-dilatation. And at this point, my question was assuming no further refinement of the population to whom this would be indicated.

Is that the case, Dr. Cigarroa and Dr. Slotwiner?

DR. CIGARROA: From my perspective, yes, we had commented on the differences in the language used in the IFU with regards to not luminal diameter but the patency at follow-up.

DR. PAGE: And, Dr. Slotwiner, were you limiting the patients for whom this was indicated?

DR. SLOTWINER: No, but I think being fully transparent in the labeling with the limitations that were discussed is --

DR. PAGE: And I think all of us have an asterisk in terms of wanting more information -- we're going to be talking about that -- if we were to go to a post-approval study.

Dr. Lange, did you want to comment?

DR. LANGE: I do.

I'm interested -- for approval in the U.S. is the experience in the United States patients, and there were only 252 in the study; only 167 got the drug coated balloon versus 85 with the PTA. So I don't have enough data to say it's more effective. I have no hints that it's not as safe or that it is less

effective than a routine balloon, so I think it's a good alternative. There's just enough data available to say it is more effective, but it is an alternative.

DR. PAGE: So you're saying yes, safe; no, not better. But yes, it is a clinically acceptable alternative?

DR. LANGE: It is. It is at least as effective as a routine balloon, so it's no less effective. But I can't say, in the U.S. population, it is more effective based upon the data we have. It is effective, though.

DR. PAGE: Comments from the Panel further on the question I posed, or anybody take a contrary perspective to Dr. Lange?

Dr. Somberg.

DR. SOMBERG: I resist taking a contrary perspective.

(Laughter.)

DR. SOMBERG: I mean, to anybody. So don't feel singled out here. Well, I think we talked about poolability, and you have to either have a consistent approach or no approach. And my approach would be that it is poolable, the data. We have to take the U.S. data and the OUS data together, and we have to talk about efficacy. And it is suggested that there's a modest -- not even suggested. There is a modest effect.

The design of the study was such that it met its primary prespecified endpoint, and on that basis, I think we could satisfactorily recommend it as potentially superior in a select population. That's what we can always do with studies because it doesn't represent the entire

population; it represents what you target.

At the same time, what you say for efficacy, you can change for safety, and it's not inconsistent to say that because we do not have a signal of efficacy in the U.S. female population, that -- well, we can warn people it hasn't been established. That's not saying leave them out. So my difference with the Chairman is such that it's not saying leave them out or exclude women or tell the interventionists not to do them. It's just saying be aware that that dataset is just less secure than the others.

DR. PAGE: Other comments before I try to summarize for Dr. Zuckerman?

(No response.)

DR. PAGE: Dr. Zuckerman, with regard to Question 7a and 7b, we've already given you the response. With regard to Question 7c, I'm hearing uniformity in terms of safety, I believe.

The efficacy, I think, generally people are favorably disposed, although there is some concern about subgroup analysis and specifically the U.S. population, where we are responsible.

And in terms of being an acceptable alternative, it is seen as an acceptable alternative as adjunctive therapy, which is modestly effective.

Is that satisfactory?

DR. ZUCKERMAN: Yes, that's a very good summary.

DR. PAGE: Great. So we'll move on to the hypothetical post-

approval study. As has been said many times, the fact that we're discussing this doesn't have any implication whatsoever as to whether this device will be approved. I draw your attention to page 8 and 9.

And I will now ask Ms. Pack to read both Questions 8a and 8b for us.

MS. PACK: Question 8:

a. Keeping in mind all of the issues raised with the existing studies (e.g., potential bias, gender and geography interactions, the diminished treatment effect at 730 days, and the limited study follow-up time points), please comment on the adequacy of the proposed post-approval study for long-term follow-up of the existing study cohorts. Specifically, please indicate if a new enrollment study is recommended to address unresolved concerns.

b. Please indicate if there are additional questions beyond the longer-term performance of the Lutonix DCB that you think should be evaluated as part of the post-approval study.

DR. PAGE: Okay. We've had a very nice discussion of a number of issues, so I'll look to the Panel to just, in a word or two, mention the analyses that need to be undertaken and perhaps the duration of study.

Dr. Somberg.

DR. SOMBERG: Well, I think we need a little bit larger sample

and with emphasis on U.S. women, and we need to pursue maybe not as many -- certainly not as many as this study did, as the pivotal study did. But what should I say, symptom endpoints? And not just be a patency issue, because while we all assume patency is important, we do not know that it is a true surrogate endpoint. That's not been a demonstrated surrogate.

So I think we have to try to collect other information that would, I think, work to both the patient and the Sponsor's benefit because if it really improves walking time, it really improves symptomatology. You would have a much better product, much more utilized, and we would be remiss not to use it more in the medical practice.

DR. PAGE: Thank you.

What would others add to Dr. Somberg's modified post-approval study?

Yes, Dr. Gravereaux.

DR. GRAVEREAUX: We would have to recognize that this very well-done study is limited to a sample of the patients with PAD; it's a claudication, non-critical ischemic study that may have a big question about future use for this platform and critical limits can be -- so as a future potential thing to look at would be an expansion, instead, of the Task A and B lesions and looking at the use for different anatomic variant of disease.

There was, I think, 20% total occlusions here, so it's mostly stenoses, which goes along with why it was, again, successful as balloon

angioplasty because it didn't require as much scaffolding. But longer Task C and D lesions would be something which are not addressed in this current iteration.

DR. PAGE: So are you recommending analysis of use that's in patients that have not previously been studied or getting more numbers of the small groups that were studied within this trial?

DR. GRAVEREAUX: Well, this indication is in Rutherford -- you know, it explained Rutherford 2 through 4, so it doesn't include traditionally a high level or high amount of critical and ischemic patients. So it's in non-threatening -- in a limb disease.

DR. PAGE: Dr. Zuckerman.

DR. ZUCKERMAN: Yes. So Dr. Gravereaux, as an expert interventionalist, has noted many times today that this is a promising therapy and that there is a real need to study it in higher risk patients who don't do well with current therapeutic modalities. The Agency would be happy to entertain those sorts of IDE studies; they are needed from a public health perspective, and they can be easily initiated.

But what we're looking for right now is a post-approval study that's well designed within our intended indications, and Panel members have pointed out that we certainly need a better study design to look at U.S. female results.

Dr. Hirshfeld, I would like you to specifically comment on the

length of the study. Right now the Sponsor only wants to go out to two years, but I could foresee, by three or four years, that there's no treatment difference between control and experimental device. So can you help us on the duration issue?

DR. HIRSHFELD: Well, first of all, all Kaplan-Meier curves eventually get to the zero line if you follow them long enough. And so the real significance of the Kaplan-Meier difference is the bubble between the two curves during the time that the bubble exists. I think 12 months is short; 24 months sounds a little bit better to me than 12 months, and I think it would be unreasonable to expect something that would be lasting three to four to five years, given the nature of this population.

DR. PAGE: Just so I'm clear, you don't think it would be unreasonable? That was a double negative? Are you advocating going three, four, or five years?

DR. HIRSHFELD: I think it would be reasonable to look for effect in the two- to three-year range. I think beyond three years, I think these people who have so many comorbidities are likely -- we're likely to lose a lot of patients in that time frame.

DR. PAGE: In terms of the duration, in terms of this being in part a drug trial, I've heard Panelists, I believe, today comment on going further than that. Is there any sentiment in the Panel that they should be followed beyond two or three years?

Dr. Somberg and then Dr. Posner.

DR. SOMBERG: Well, it's not just from the pharmacological vantage point, but certainly that's one aspect. But, I mean, we're talking about a registry. I completely agree with you if it was a study. In fact, 12 months is a reasonable point for this type of study. But I think there's no reason, if you start following people, to close your registry down. And if I heard, there's a technical issue here about IRB approval for two years and what are we going to do with the study after two years? You get a telephone follow-up. Well, that's useful to some extent, and I would go with that. Or you can try to re-consent patients. If no one signs a consent, that's a good signal that things aren't working well, and if everyone signs a consent, it's another good signal.

DR. PAGE: Dr. Simon and then Dr. Cigarroa.

DR. SIMON: Sure, just on this issue. I was wondering if Dr. Zuckerman could just inform us, how is the long-term patency issue that goes into the two-, three-year window, how was that handled in the Zilver study and some of these other studies where it just is a pressed endpoint?

DR. ZUCKERMAN: I would like Dr. Cavanaugh, Dr. Lim, or Ms. Pack to comment on the length that we generally use for some of our peripheral vascular device studies.

Ms. Pack, do you want to begin?

MS. PACK: Sure. So for the device specifically that you

requested, for the Zilver, the primary effectiveness endpoint was out to three years. However, there was safety evaluation out to five years, primarily for the drug-related effects.

DR. SIMON: I mean, it's just helpful to sort of see that in the context of -- I mean, it's similar disease pathology, certainly, and it's how we're viewing these other devices, so I don't think it's -- it is reasonable to see how it's handled elsewhere.

DR. PAGE: So your inclination is go longer, perhaps three to five years?

DR. SIMON: Well, I guess I want to acknowledge that getting into sort of a five-year time frame becomes somewhat difficult, as an operator, to acquire that data. I mean, I think we should make an effort to collect maybe a registry as an adequate approach.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: I think, from my perspective, I would say that two years is probably reasonable, that what we need here is a larger sample size. I think that in terms of restenosis, the vast majority of restenotic processes occur within 24 months. Beyond that, there is disease progression related to the comorbidities, et cetera.

I think that the longer-term period beyond two years with regard to the drug is for very rare adverse events related to the drug, and there are corollaries in other disease states where that drug has been

administered for a long time. So I think the yield is exceedingly small with regards to the adverse safety, and I would argue larger sample size and the registry, 24 months.

DR. PAGE: Thank you.

Dr. Posner, and then I'm going to try to summarize.

DR. POSNER: Dr. Cigarroa hit the nail on the head again, and I'll point out that we've already dropped down to 400 people at two years. At three years, there won't be that many more. You'd be losing more and more. And for the drug safety, it goes to the pharmacokinetics, how long is that drug going to be around to give you any more effects. As things are happening, it's going to be progression of disease rather than the drug that was initially given, unless it's like DMS or something that's going to give you something 10 years down the road. So I think the two years looks pretty good.

What I would like to see is as new people are given the treatment, if it's approved, that the data is collected, particularly for women and the questions that are asked are some of the questions that we asked today that weren't answered, which is hormone levels, why they stopped walking at a certain distance, et cetera, et cetera. And so I would improve the initial collection data for the new people that are going to be given this treatment, but I think for the long-term follow-up on the initial group, I think two years is fine.

DR. PAGE: So, Dr. Zuckerman, if I may summarize. I think there's unanimity that more patients need to be collected and that specifically we want to know more about longer-term in U.S. women and we really ideally understand the issue of the relationship to smoking. Some sort of relevant clinical endpoint would be nice, at least covered over the first couple of years. The duration of the study, there's a variety of opinions. At the very minimum, two years, but I'm hearing several -- and myself included -- who would push it further, consistent with other studies, follow-up of this nature of device.

Is this helpful to you?

DR. ZUCKERMAN: This is a very helpful discussion and summary.

DR. PAGE: I might not have gotten that right.

Dr. Cigarroa and Dr. Lange both have their hands up.

Dr. Lange.

DR. LANGE: Just one quick thing. The number of control patients you have is very small. It's 85 right now in the U.S. It's going to diminish. What I would encourage FDA to do is see if there are other trials where there are similar entrance criteria that you can use their control patients for comparison.

DR. ZUCKERMAN: Great suggestion.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: One comment with regard to the duration of follow-up that I failed to mention that influenced the shorter period is the fact that there's not a permanent implant. The issue of not implanting a stent with the associated possibility of metal fatigue and fracture and those problems are not present in this population as treated.

DR. PAGE: Great, thank you.

With that, it's time for FDA and Sponsor summations. At this time, the Panel will hear summations, comments, or clarification from the FDA. And you have 10 minutes. And we'll put nine minutes on the clock with one minute warning, please.

DR. LIM: I can do it in nine.

(Laughter.)

DR. PAGE: I'm not rushing you.

DR. LIM: So my name is Lisa Lim. I am the Chief of the Peripheral Interventional Devices Branch. So, first of all, thank you for participating in this important Panel meeting for a first-of-a-kind combination product and for your thoughtful comments on the information presented here today.

As you know, FDA is charged with determining if there is reasonable assurance of safety and effectiveness based on the information provided in support of approval. In making this determination, FDA considers the totality of the data as well as whether or not the benefits outweigh the

risks for the intended population.

Here are the key messages from our presentation today: The study met its primary endpoints for safety and effectiveness for the prespecified primary analysis population. However, the predefined success criteria were not met for other analysis populations and for key secondary endpoints.

There are also some surprising findings regarding the impact of gender and geographic differences on outcomes. While these differences are significant from a statistical standpoint, the clinical significance is not clear. In addition, it is not clear if the differences should be explored prior to approval from marketing or if they could be explored after approval, if warranted.

We ask the Panel to consider these topics as well as the other issues presented today when deciding whether the data demonstrate a reasonable assurance of safety and effectiveness, and whether the benefits outweigh the risks for the intended population in determining if this product should be made available as a treatment option for these patients.

Thank you.

DR. PAGE: Thank you very much.

DR. ZUCKERMAN: Okay, we aren't quite finished, I think.

(Laughter.)

DR. ZUCKERMAN: That was an excellent discussion by Dr. Lim,

and I really want to congratulate the Panel on a very thorough analysis of the data at hand. And so before Dr. DeFord begins in a few minutes, I would like him to take a few minutes to consider what specific indication he would like the Panel to vote on in a few minutes as part of his remarks. For example, is he comfortable with the spirit of the current indication, or does he feel more comfortable at this point taking out inclusion of women. This is important for Dr. DeFord and his team to consider because we only are able to vote once, and then we go home.

So take a few minutes before you come up to the podium, Dr. DeFord.

DR. PAGE: Dr. Zuckerman, as he's considering that, I think it may be valuable to have further discussion within the Panel as to whether that's something that would be welcome to the Panel. Is that fair?

DR. ZUCKERMAN: That's very appropriate.

DR. PAGE: So before we move on with that, I'm interested in looking around at the Panel to see whether you are lumpers or splitters here in terms of the indication. We only have one vote, and I'm hearing consensus that this sounds to me like it's something that is approvable, but we have not taken a vote yet, and I think it is important because Ms. Chauhan was very valuable in emphasizing the issue of what happens with women; and two sides of the coin, one being do we have enough data to include them, and the other being do we basically say that this isn't indicated for them and then if,

indeed -- the statistical issue -- we have kept them from having valuable therapy. So not to bias the perspective of the committee at all. I think we should get an idea of a sense of the committee.

Dr. Somberg.

DR. SOMBERG: Well, first, I want to establish I come from Chicago, so we vote often and often --

(Laughter.)

DR. SOMBERG: -- and many times. Okay. There's a long history of that. With that established, I think we should compromise, and I would not be in favor of -- have it cut out and excluding women, if we do recommend this, not recommending it for women.

At the same time, I do not believe the data is strong for women. In fact, it was going in the wrong direction. Everything else is trending, we have consistency; so I've said that before. So I think we should just have something to the effect -- and if I recall, my statement is: Warning: Women with severe disease, efficacy has not been established for the DCB. Not that you shouldn't use it, but it just hasn't been established.

So we overall approved it based on the aggregate of the trends, and then the physician and the patient should individualize. And I think that's what our Consumer Representative would be most comfortable with, I think, because then it sort of initiates a discussion as opposed to placing it in some scientific point in the Panel Pack.

DR. PAGE: Nicely stated.

Dr. Cigarroa and then Dr. Simon.

DR. CIGARROA: So this is a recurrent issue at multiple panel meetings, and that is subgroup post hoc analysis in which gender or country seems to have an impact with the differential clinical outcome. And, statistically, we're underpowered. I would vote being a lumper here and have data through postmarket study, registry.

DR. PAGE: Thank you.

Dr. Simon.

DR. SIMON: Yes. As an operator or someone who would maybe be talking with Ms. Chauhan, I think the strongest text I would use here -- because I sometimes think when the FDA puts things to paper, it's almost Talmudic or it's like it becomes law and people really scrutinize it -- would just be to say not proven in women so that you maybe tip someone's hand to have a discussion because, certainly, I think it's too strong to go beyond something like that in terms of a warning.

DR. PAGE: Fair enough.

Let me take a swing at this, then, because we do need to move on and the Sponsor needs to deal with the question of potentially changing their indication. Might I suggest that the indications, as written in one sentence or another, not include anything about women or any other subgroup outside the U.S., smoker, whatever; but it be clear in one form or

fashion that at this time data are not significant in terms of demonstration of efficacy in women, and as such, it does clearly make the point that the operator needs to consider the data.

This is a lumper's perspective in terms of the indication, but acknowledgement of the fact that there isn't just a failure to find statistically significant effect in women, but actually it's going in the wrong direction this time and there is concern among the Panel. I see hands, but I want to look toward the Panel in terms of whether there's general comfort there.

Dr. Posner.

DR. POSNER: And we're working on activated patients and patients making decisions right now in Hartford Foundation. And what you said is absolutely right, and I would just add one thing and say because of the small numbers of women in the initial study and then go on with what you said, so that a female patient going in and talking to her physician --

DR. PAGE: I'm scared of wordsmithing too much because I don't know that it's because there aren't enough women; I don't know that there isn't a real failure of effectiveness in women. But we just can't say one way or the other.

DR. POSNER: Right. But for the patient coming in to make that decision, they're going to ask for that information or they should ask for --

DR. ZUCKERMAN: Dr. Posner and Ms. Chauhan, where we are in the Panel discussion is a little bit unusual right now. We do have to allow

Dr. DeFord to sum up. I think that this discussion, ancillary discussion, has been extremely helpful for helping Dr. DeFord prepare his last statements, but I'm going to ask the voting members to give Dr. Page either a nod of support or indicate that they don't support his summary, but we do need to move to Dr. DeFord's closing comments now.

DR. PAGE: Thank you.

I'm looking at the Panel. I'm seeing nods. I'm even seeing a thumbs up and a wave.

(Laughter.)

DR. PAGE: So not the wave, but a wave.

So what we're seeing here, Dr. Zuckerman, is the Panel would be receptive to the indication being gender neutral as opposed to asking Dr. DeFord to make his decision now for the one vote that this Panel can give.

DR. ZUCKERMAN: Thank you.

DR. PAGE: I now welcome the Sponsor for a 10-minute or less summation, and the clock will start as soon as you get started.

DR. DeFORD: Thank you very much.

And so just to start, based on the data that we have to date, we also believe the indication we presented is acceptable with the addition of the pre-dilatation that we had discussed before. Also on behalf of Bard, the investigators, and most importantly, the patients who graciously volunteered in the hope of advancing clinical medicine, I'd like to thank the Chairman, the

Panel, and the FDA for the careful, thoughtful preparation and deliberation of the Lutonix DCB today.

Our goal was simple. We sought to enhance safety and sought to enhance standard PTA for a vulnerable class of patients by combining two known technologies to improve patency. Our study also demonstrated non-inferior safety and consistent and encouraging trends and secondary endpoints. We believe physicians need effective and safe options to treat diseased arteries without leaving behind a permanent implant. From the results of our clinical trial, the Lutonix DCB, we believe, offers a viable alternative to standard PTA.

Thank you.

DR. PAGE: Thank you, sir.

Before we proceed to a vote, I would ask Mr. Thuramalla, our Industry Representative; Ms. Chauhan, our Consumer Representative; and Dr. Posner, our Patient Representative, if they have any additional comments.

Mr. Thuramalla.

MR. THURAMALLA: Yes, I do.

To start with, I would like to compliment the Sponsor and the Agency for their very detailed presentations on a first-of-its-kind device and drug combination study. From these presentations and Panel deliberations today, we saw that the LEVANT 2 ITT results show superior effectiveness and non-inferior safety. Important thing to the sponsors of these studies, to

industry, is that the Sponsor did meet the primary endpoint.

We in industry, along with all the stakeholders, strive to do our very best to conduct a well-designed, high-quality study, and there are some lessons to be learned from the deliberations today. Some of them include appropriate patient selection with a total design of expert analysis done; sample size selection; more realistic or maybe I should say less optimistic endpoints or expectations, et cetera. Having said that, on behalf of the industry, I'd like to also request FDA to maybe potentially consider issuing a guidance document to further help and mitigate these kinds of situations going forward.

Thank you.

DR. PAGE: Thank you, sir.

Ms. Chauhan, do you have any further comments?

MS. CHAUHAN: I also appreciate the clarity of the material and the responsiveness of both the FDA and the industry to the questions we asked and the opportunity to be a part of this group.

DR. PAGE: Thank you, ma'am.

Dr. Posner, do you have any comments?

DR. POSNER: Just want to thank everybody, and this has been an incredibly informative discussion and presentation of data by both groups. And I won't say anything else. I've said enough today.

DR. PAGE: I want to thank the three of you. You bring great

value to this Panel in our deliberations. So thank you.

At this time, we're ready to vote on the Panel's recommendation to the FDA for this PMA. The Panel is expected to respond to three questions relating to safety, effectiveness, and risk versus benefit.

Ms. Waterhouse will now read the definitions to assist in the premarket approval application voting process.

Ms. Waterhouse.

MS. WATERHOUSE: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following Indications for Use: The Lutonix DCB is indicated for improving luminal diameter for the treatment of obstructive de novo or non-stented restenotic lesions in native femoropopliteal arteries having reference vessel diameters of 4 mm to 6 mm.

We will now proceed to the vote. The following questions relate to the approvability of the Lutonix DCB. Please answer them based on

your expertise, the information you received in preparation for this meeting, and the information presented at the Panel meeting.

DR. PAGE: Ms. Waterhouse, so may I read into the transcript that the indication was modified in terms of being performed after pre-dilatation? Is everybody comfortable with that, including the Sponsor?

(No audible response.)

DR. PAGE: So that's what we're voting on.

Dr. Cigarroa.

DR. CIGARROA: The other comment with regards to the IFU was instead of stating improving luminal diameter, to comment on patency at long-term follow-up --

DR. ZUCKERMAN: Okay. Dr. Cigarroa and folks, we try to stay very true to what Ms. Waterhouse has read in except when there's a major high-level point as Dr. Page has indicated. But other than that, we have to go to the vote now.

DR. CIGARROA: Thank you.

DR. PAGE: Please proceed.

MS. WATERHOUSE: Voting Question 1: Is there reasonable assurance that the Lutonix DCB is safe for use in patients who meet the criteria specified in the proposed indication?

Please use the buttons on your microphone to vote.

(Panel vote.)

MS. WATERHOUSE: Voting Question 2: Is there reasonable assurance that -- hold on one second.

DR. POSNER: Our buttons are flashing even though we're non-voters.

MS. WATERHOUSE: Okay, for Voting Question 2: Is there reasonable assurance that the Lutonix DCB is effective for use in patients who meet the criteria specified in the proposed indication?

You can please place your vote now.

(Panel vote.)

MS. WATERHOUSE: Okay, for Voting Question 3: Do the benefits of the Lutonix DCB for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet the criteria specified in the proposed indication?

Please place your vote now.

(Panel vote.)

MS. WATERHOUSE: So on Question 1, all Panel members voted yes. So the Panel voted that the data show reasonable assurance that the Lutonix DCB is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, everyone on the Panel voted yes, that there is reasonable assurance that the Lutonix DCB is effective for use in patients who meet the criteria specified in the proposed indication.

And Question 3, the Panel voted all yes, that the benefits of the Lutonix DCB outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

DR. PAGE: Thank you.

I will now ask the voting Panel members to discuss their votes. And if someone has already said what you were going to say, as we go along, you can just agree, but I do want each Panel member who voted to comment.

And I'll start with you, Dr. Simon.

DR. SIMON: My comments will be I work in this area, and there is a great unmet need here, and I wish the efficacy/safety were a little more robust, but I voted yes. I do believe in the data.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yes, I agree. I think I want to thank the Sponsor and the FDA for superb presentations, and I think the unmet need of this population played a strong role in my interpretation of the data, which had very modest effectiveness but reasonable safety, so I think that really played an important role.

DR. PAGE: Thank you.

Dr. Gravereaux.

DR. GRAVEREAUX: I also voted yes for much of the same reasons. It certainly proves to be as safe as a balloon angioplasty; possibly it

met the endpoint for mild improvement, and I look forward to seeing what it can do in the future.

DR. PAGE: Thank you.

Dr. Cigarroa.

DR. CIGARROA: Yes, for the same reasons that have been articulated.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: Again, I want to thank the Sponsor and the FDA both for excellent presentations and the responsiveness to questions and how you collaborated. And the shortcomings of the trial and the results, I think, will inform us about how to design trials a little bit better in the future.

Thank you.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: I voted yes. I was extremely concerned about the outside U.S. and about the worse results in U.S. women, but I have to say Dr. Somberg's discussions and Dr. Page's discussions and the whole idea to make sure that this doesn't go away in the labeling just totally convinced me.

So thank you.

DR. PAGE: Thank you.

Dr. Hirshfeld.

DR. HIRSHFELD: I voted yes. I have a lot of concerns about the modest level of the effect, but I am hopeful that maybe since this is a first-of-a-kind device, that this will be the genesis of further refinement of this technology that may become more effective in the future.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I voted yes for the reasons that have been well explained by my colleagues here. I urge the Sponsor to increase the robustness of the database by increasing the numbers in the registry and also to go on to areas like acute ischemia or et cetera, because I do think this is promising.

I just think the statistics is such that it turned out to be underpowered. I do all this positive thinking based on that we are going to have a preliminary concern about women in the IFU, but I do think if we build a larger database, that may turn out -- and it will be nice to know that, that that will turn out to be a non-concern.

DR. PAGE: Thank you, Dr. Somberg.

As those around the table know, I only have the opportunity to vote in the case of a tie. I don't know when I've seen unanimity in a panel for all three questions; it's been a long time, if ever, and I would agree with the Panel in their vote.

I want to compliment the Sponsor as well as the FDA for

putting together very clear, concise presentations; scrambling to answer our questions; and really operating at the highest professional level.

I want to thank our Industry, our Consumer, and our Patient Representatives for representing your own constituencies beautifully, and I want to thank the Panel for taking this business very seriously and I think coming out to the right place.

Dr. Zuckerman, do you have any further comments before I adjourn the meeting?

DR. ZUCKERMAN: No. I think you summarized it beautifully. Everyone did an awesome job today, and I especially want to thank Dr. Page for leading us through a very difficult dataset.

Thank you.

DR. PAGE: Thank you.

And with that, this June 12, 2004 [sic] meeting of the Circulatory System Devices Panel is adjourned. Have a great evening.

(Whereupon, at 5:20 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

June 12, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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